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Benzimidazole-carboxamides as potent and bioavailable stearoyl-CoA desaturase (SCD1) inhibitors from ligand-based virtual screening and chemical optimization

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ABSTRACT

The discovery of potent benzimidazole stearoyl-CoA desaturase (SCD1) inhibitors by ligand-based virtual screening is described. ROCS 3D-searching gave a favorable chemical motif that was subsequently optimized to arrive at a chemical series of potent and promising SCD1 inhibitors. In particular, compound **SAR224** was selected for further pharmacological profiling based on favorable in vitro data. After oral administration to male ZDF rats, this compound significantly decreased the serum fatty acid desaturation index, thus providing conclusive evidence for SCD1 inhibition in vivo by **SAR224**.

The increasing prevalence of obesity and associated metabolic disorders such as type 2 diabetes in societies following a Western lifestyle highlights the necessity to discover new pharmaceutical solutions for this area.[1,2] Recently, elevated activity of stearoyl-CoA desaturase (SCD1), one of the essential enzymes in lipogenesis, has been linked to the pathogenesis of obesity, metabolic disorders, dyslipidemia and type 2 diabetes.[3,4] SCD1 is an iron-containing microsomal enzyme, which catalyzes the formation of a *cis*-double bond at the carbon-9 position of saturated fatty acyl-Coenzyme-A esters, the rate-limiting step in the synthesis of mono-unsaturated 16:1 n-7 and 18:1 n-9 fatty acyl-CoAs.[3] SCD1 expression is regulated by different nutritional and pharmacological stimuli.[5,6] SCD1-deficient mice were reported to exhibit reduced body weight, body fat mass, increased oxygen consumption and improved insulin sensitivity in a glucose tolerance test.[7] Therefore substantial efforts in the pharmaceutical industry have been undertaken to discover small-molecule SCD1 inhibitors for the treatment of metabolic disorders.

In a previous publication we reported the discovery and pharmacological profiling of **SAR707** as a promising member of a class of potent hexahydro-pyrrolopyrrole based SCD1 inhibitors (Fig. 1).[8,9] Our starting point was patent applications from Xenon Pharmaceuticals[10] and Merck Frosst Canada,[11] describing chemical series reported to modulate SCD1 activity, thereby regulating plasma-lipid levels. Further structure–activity relationship data for SCD1 inhibitors was also available in reports from Abbott Laboratories.[12,13]

Rescaffolding the central piperidine substructure resulted in the discovery of the hexahydro-pyrrolopyrrole scaffold,[9] which subsequently was optimized to result in **SAR707** with an IC_{50} value of 0.00848 μM in a rat liver microsome SCD1 assay.[8] In particular, this compound is characterized by high potency, selectivity and favorable properties in enzymatic and cellular assays. In vivo, **SAR707**

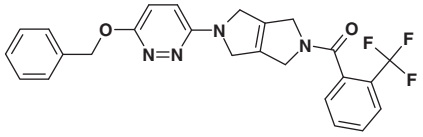

Figure 1. Chemical structure of SAR707.

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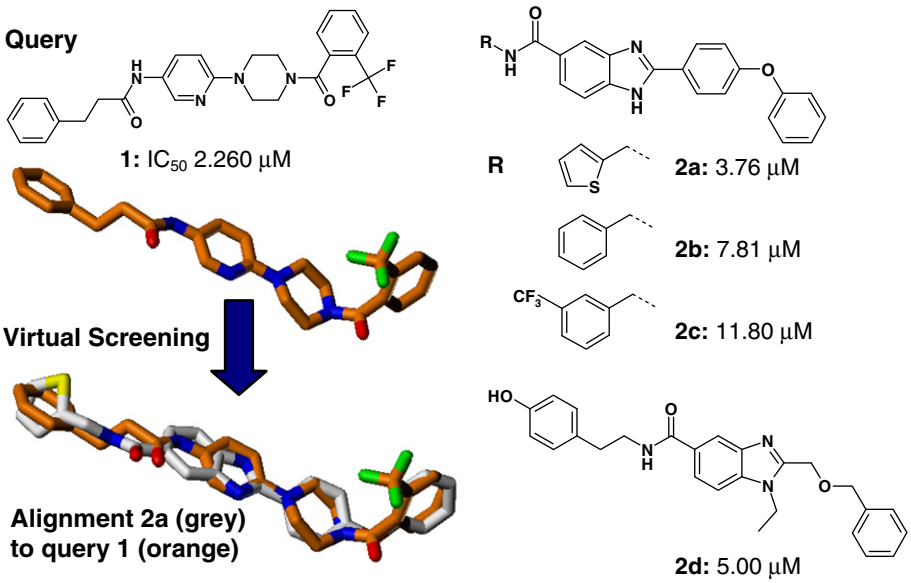
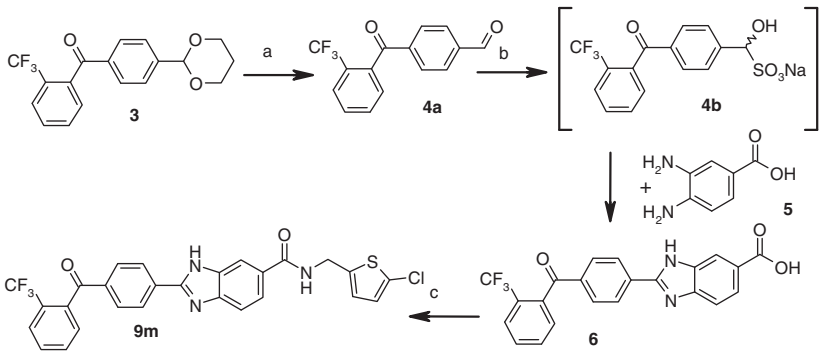


Figure 2. Ligand-based virtual screening. Left: ROCS alignment of hit structure **2a** (grey carbons) to query **1** (orange carbons). Right: Chemical structures for hit **2a** and analogs from further iterations.



Scheme 1. Synthesis of compound **SAR224**. Reagents and conditions: (a) AcOH/H_2O 80/20, 65 °C, 90 min, 73%; (b) $Na_2S_2O_5$ (1.3 equiv), DMF, 100 °C, 1 h, 79%; (c) HOBt, EDC·HCl, DIEA, DMF, rt, 18 h, 95%.

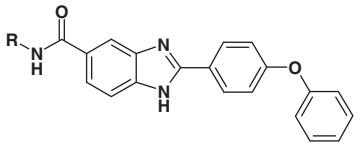
reduced the serum desaturation index, decreased body weight gain and improved lipid parameters and blood glucose levels in obese Zucker diabetic fatty rats treated for 4 weeks in a chronic study.[8] However, fissures of the eyelid, alopecia and inflammation of the skin were observed in parallel from day 11 onwards in all animals treated with the same metabolically active dose.[8] Therefore, unfortunately, the benefits of systemic in vivo SCD1 inhibition by this compound were accompanied by dose-dependent adverse effects.[8]

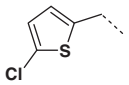
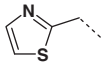
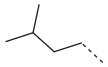
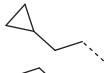
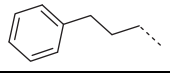
This observation prompted us to identify alternative chemotypes as SCD1 inhibitors. In this publication, we describe the discovery of potent benzimidazoles using ligand-based virtual screening, followed by optimization of a favorable motif to arrive at the potent and promising compound **SAR224**, suitable for further pharmacological profiling.

Ligand-based virtual screening[14] was performed in multiple iterations guided by experimental data. For the first iteration, the query molecule **1**[10] with an in-house IC_{50} value of 2.26 μM was used for a 2D similarity search using UNITY,[15] a topological pharmacophore search using an in-house implementation of CATS,[16] and a 3D shape search using ROCS.[17] For ROCS, a canonical 3D geometry served as query; hits were selected using the *Combo-Score*. For each method, searching was performed in our corporate database.

All hit lists were combined and filtered by physicochemical properties. 148 compounds were selected after visual inspection

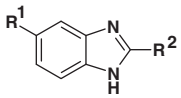
Table 1
In vitro SCD1 inhibition for compounds **7a–7f**[a]

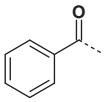
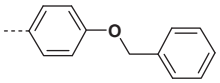
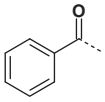
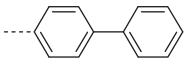
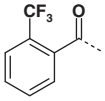
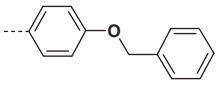
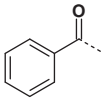
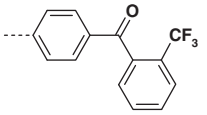
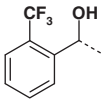
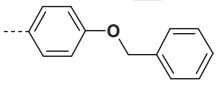
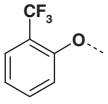
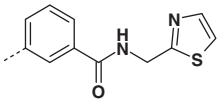
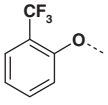
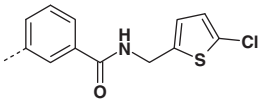


Compd	R	SCD1 IC_{50} (μM)
7a		3.70
7b		6.51
7c		16.6
7d		21.6
7e		24.9
7f		28.3

[a] IC_{50} data were obtained as described in the text and in Refs. 8,9,19.

Table 2
In vitro SCD1 inhibition for compounds **8a–8g**[a]



Compd	R^1	R^2	SCD1 IC_{50} (μM)
8a			15.8
8b			>100
8c			13.3
8d			>100
8e (rac)			0.082
8f			1.30
8g			2.21

[a] IC_{50} data were obtained as described in the text and in Refs. 8,9,19.

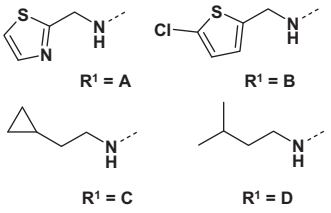
and tested for SCD1 inhibition and 31 of these compounds were found active (21%). From a total of four novel scaffolds, compound **2a** (IC_{50}: 3.76 μM) with a benzimidazole-carboxamide scaffold was regarded as a promising start for further investigation. This structure resulted from the ROCS search; its alignment (grey carbons) with the query **1** (orange carbons) is shown in Figure 2 (left).

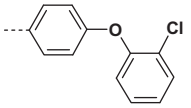
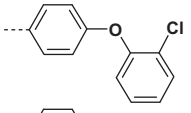
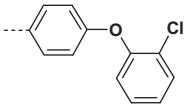
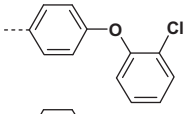
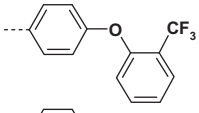
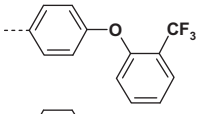
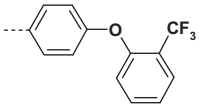
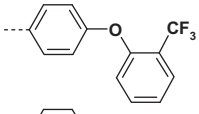
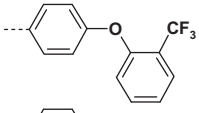
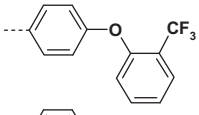
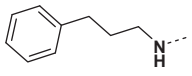
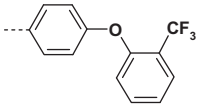
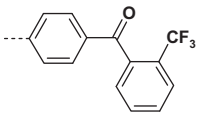
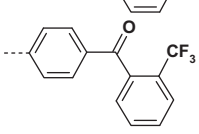
In a second iteration, 103 analogs of the hits were retrieved by 2D similarity searching (UNITY). A total of 15 compounds were active after experimental testing (15%). This resulted in the discovery of further benzimidazole-carboxamide analogs of **2a**, summarized in Figure 2 (right panel). Replacing the thiophene by benzyl groups resulted in only slightly decreased SCD1 activity (**2b–c**). Alkyl-substitution at the imidazole N1 combined with alkyl instead of aryl-substitution at carbon C2 was also tolerated by the enzyme (**2d**).

Ligand-based virtual screening was then continued using additional actives from in-house investigations and the literature, which finally resulted in 57 hits for a total of 961 compounds tested (6%). We then decided to investigate the structure–activity relationships of novel substituted benzimidazoles with a limited medicinal chemistry program due to their interesting computed physicochemical properties (**2a**: $\log D_{7.4}$[18]: 3.68; MW: 425; ligand efficiency: 0.24; lipophilic ligand efficiency: 1.74), alignment to the query molecule **1** (cf. Fig. 2) and chemical attractiveness (cf. Scheme 1).[19]

The synthetic pathway for the preparation of compound series **7–9** is based on the formation of the benzimidazole ring by a microwave accelerated cyclodehydration from substituted aro-

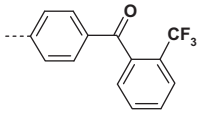
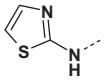
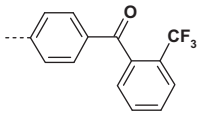
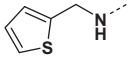
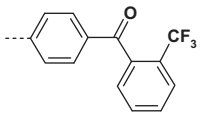
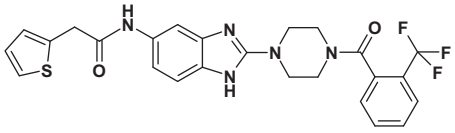
Table 3
In vitro SCD1 inhibition for compounds **9a–9q**[a]



Compd	R^1	R^2	SCD1 IC_{50} (μM)
9a	A		0.115
9b	B		0.832
9c	C		0.966
9d	D		2.72
9e	A		0.212
9f	B		0.142
9g	C		0.539
9h	D		0.434
9i	CH_3NH–		27.2
9j	CH_3CH_2O–		38.3
9k			>100
9l	A		0.078
9m (SAR224)	B		0.136

(*continued on next page*)

Table 3 (*continued*)

Compd	R^1	R^2	SCD1 IC_{50} (μM)
9n	D		3.86
9o			4.52
9p			0.099
9q			3.20

[a] IC_{50} data were obtained as described in the text and in Refs. 8,9,19.

matic 1,2-diamines and aldehydes. As a representative example, the preparation of benzimidazole amide **SAR224** is depicted in Scheme 1. The synthesis starts with a mild acidic hydrolysis of the commercially available dioxolane **3** to unmask the aldehyde moiety. Subsequent microwave-assisted cyclization of the sodium bisulfite adduct **4b** of benzaldehyde **4a** with 3,4-diaminobenzoic acid **5** provided benzimidazole **6**.[20] Finally, the carboxylic acid was amidified with 5-chloro-2-thiophenemethanamine to yield the targeted SCD1 inhibitor **9m** (**SAR224**).

Table 1 summarizes a set of benzimidazole-carboxamides **7a–7f** with a biphenylether motif on carbon 2 with their corresponding SCD1 inhibitory potencies [μM]. The IC_{50} values were evaluated in a rat liver microsomal assay using ^{14}C-labeled stearic acid, an 8-point concentration range and calculated as previously described.[8,9,19,21] All compounds were tested up to a concentration of 100 μM. Compounds with an IC_{50} >30 μM were considered as 'inactive'.

We first focused on the role of the amide substituent on the left side of the scaffold. The SCD1 inhibition is maintained when a chlorine atom is added to the thiophene of **2a** (**7a**: 3.70 μM). Replacing the thiophene by a thiazole results in decreased activity by a factor of 2 (**7b**: 6.51 μM), while aliphatic substitutions consistently lower the activity, as exemplified by **7d** with an isopentyl-substituent (IC_{50}: 21.6 μM).

Next, we studied the influence of the carboxamide linker on SCD1 activity with a small set of compounds, which are summarized in Table 2. Replacing the carboxamide by a keto-linker included in a benzophenone moiety does not improve activity, as shown for derivatives **8a**–**8d**. Adding a CF_3-group at the ortho-position does not significantly improve activity, as can be seen by comparing compounds **8a** and **8c** with IC_{50} values of 15.8 versus 13.3 μM, respectively.

However, replacing the keto-linker with a hydroxyl-group as in **8e** (racemic mixture) results in a significant improvement of activity (IC_{50}: 0.082 μM). Due to the chirality of this motif and its higher metabolic lability, this motif was not followed further. Finally, we introduced an ortho-trifluoromethyl-phenoxy-substituent on this position of the benzimidazole. The rational of derivatives **8f** and **8g** was to check if a reversed superposition compared to the alignment in Figure 2 of the benzimidazole (grey) with the virtual screening query **1** (orange) could be possible and whether

Table 4
In vitro cell activity[a], physicochemical and ADMET data for selected SCD1 inhibitors

Compd	HepG2 IC_{50} (μM)	H4IIE IC_{50} (μM)	ACC Phosphorylation (HepG2)	Caco-2 Ptmax ($\times 10^{-7}$ cm/s)	MLab Rat (% labile)	MLab Mouse (% labile)	MLab Human (% labile)	MLab Keto (% labile)	MLab Quin (% labile)	log $D_{7.4}$ (calcd)[18]	log $D_{7.4}$ (exp)	Ligand efficiency	Lipophilic ligand efficiency
8e	0.295	0.014	252	182.3	20	-	71	46	60	5.29	–	0.28	1.79
9a	1.16	0.305	211	63.6	38	23	45	16	40	3.85	2.24	0.30	3.08
9b	1.36	–	173	113.8	31	36	64	41	62	4.73	–	0.25	1.35
9c	2.34	–	140	166.8	38	49	62	45	58	4.24	–	0.26	1.77
9e	0.313	–	177	–	–	–	–	–	–	3.75	–	0.26	2.92
9f	0.439	–	287	–	–	–	–	–	–	4.62	–	0.26	2.22
9l	0.179	0.104	211	–	–	–	–	–	–	2.92	–	0.27	4.18
9m (SAR224)	0.157	0.182	280	52.6	40	–	45	10	40	3.80	3.94	0.25	3.07

[a] IC_{50} data were obtained as described in the text and in Refs. 8,9,19.

a CF_3-group would improve binding affinity. While derivatives **8f** and **8g** exhibit a slightly increased activity with 1.30 and 2.21 μM compared to the original hit, this option was not explored further with a larger range of R^2 substituents, since alternative substituents combined with the carboxamide linkers lead to significantly improved activity (cf. Table 3).

Table 3 summarizes our efforts to investigate the ortho-position on the distal phenoxy-moiety of the original hit **2a**. The ROCS-derived alignment of **2a** with the virtual screening query **1** suggests that inserting the lipophilic substituent of the query **1** at this position in our series should be tolerated by the enzyme. We explored this option combined with different carboxamide substituents (R^1 in Table 3). Introducing an ortho-chlorine substituent on the distal ring with a thiazolyl-substituent attached to the carboxamide (R^1 = A) results in potent derivatives, for example, **9a** (IC_{50}: 0.115 μM).

The nature of the amine substituent of R^1 significantly influences SCD1 activity. Replacing the thiazole-ring by a chloro-thiophene (R^1 = B) results in a lower activity (**9b**: 0.832 μM), while aliphatic substituents do not improve activity, as demonstrated by **9c** and **9d** with IC_{50} values of 0.966 and 2.72 μM, respectively.

Interestingly this ranking of R^1-substituents is not respected if the ortho-chlorine of substituent R^2 is replaced by an ortho-trifluoromethyl group. Here the most active compound is obtained with the chloro-thiophene moiety (R^1 = B), **9f** (IC_{50}: 0.142 μM) rather than with the thiazolyl-moiety, **9e** (IC_{50}: 0.212 μM). Combining aliphatic R^1-substituents with ortho-CF_3-substituted biarylethers does not improve activity, as seen by compounds **9g** and **9h** with IC_{50} values of 0.539 and 0.434 μM, respectively. Replacing the R^1-carboxamide substituent by a methyl-group significantly affects activity (**9i**: 27.2 μM), and even more so with a phenylpropyl-substituent (**9k**: >100 μM). A similar decrease in activity is observed for the corresponding ethyl-ester substitution at position R^1 (**9j**: 38.3 μM).

Finally we replaced the ortho-substituted biphenylether by substituted benzophenone-derivatives (**9l–9q**). Our intention was to explore the effect of altered hydrogen-bond accepting properties on SCD1 inhibition by comparing the carbonyl oxygen to the aromatic ether-oxygen which cannot play the role of H-bond acceptor. Once again the most significant influence on activity is observed with a thiazole-substituent (R^1 = A; **9l**: 0.078 μM) and chloro-thiophene (R^1 = B; **9m**: 0.136 μM), while aliphatic substituents at R^1 once more result in decreased SCD1 inhibition (**9n**: 3.86 μM). These favorable motifs in **9l** and **9m** were further explored by changing the distance between the aromatic thiazole ring and the carboxamide linker.

Removing the methylene-linker from R^1 = A reduces activity, as can be seen by comparing **9l** (IC_{50}: 0.078 μM) and **9o** (IC_{50}: 4.52 μM. Removal of the chlorine substituent in **9m** has only a slightly favorable effect on SCD1 inhibition, leading to **9p** with an IC_{50} value of 0.099 μM. Our final investigation in this series was to reverse the order of the carboxamide linker, resulting in the much less active compound **9q** (3.20 μM).

This systematic SAR investigation had lead to several molecules that were interesting as potent SCD1 inhibitors, and which were then profiled in further assays. A summary of additional in vitro data, giving cellular SCD1 activities in rat H4IIE and human HepG2 liver cell lines, effect on ACC phosphorylation in human HepG2 cells (at 10 μM concentration with in-cell Western immunolabeling),[8] ADME and physicochemical properties is provided in Table 4. In general, the entire chemical series is characterized by high Caco-2 permeability and acceptable to moderate metabolic lability rates (e.g., column *MLab Human* reporting the percentage of a compound metabolized). Addition of the CYP3A4/5 inhibitor ketoconazole to the metabolic lability assay reveals an important influence of CYP3A4/5 on the observed metabolic degradation of the compounds (column *MLab Keto* in Table 4). In contrast CYP2D6 apparently is much less likely to be involved in this metabolization process, as the addition of the CYP2D6 inhibitor quinidine (column *MLab Quin* in Table 4) does not significantly alter the experimentally observed metabolization rates. From the inspection of Table 4, compound **9m** exhibited interesting in vitro ADMET and physicochemical properties with moderate human metabolic lability and still acceptable $\log D_{7.4}$. This compound is the most potent member of this series in HepG2 and H4IIE cell-based SCD1 assays with IC_{50} values of 0.157 and 0.182 μM (see Table 4), respectively. It was also potent with respect to ACC phosphorylation. Therefore, this compound was selected for further investigation and renamed **SAR224**.

An in-depth pharmacokinetic and pharmacological characterization of **SAR224** was performed. All experimental procedures were conducted in accordance to the German Animal Protection Law and international animal welfare legislation and rules and performed as previously described.[8,9,19] After intravenous administration of 5 mg/kg **SAR224** in solution to male ZDF rats, a low mean plasma clearance (0.25 L/h/kg), a large volume of distribution (V_{ss} = 1.7 L/h/kg) and a long half-life (6.5 h) were observed. After a single oral dose of 30 mg/kg **SAR224** in suspension to male ZDF rats, the mean plasma concentration profile showed a slow increase from 0.25 to 6 h after administration and a mean C_{max} value of 1950 ng/mL after 4 h. **SAR224** showed a long mean apparent plasma half-life (8.4 h) and a relative bioavailability of 25% (Fig. 3, Upper). To evaluate the in vivo pharmacological activity of **SAR224**, the compound was administered once orally at 30 mg/kg to 8 week-old male ZDF rats, a well-known animal model of obesity and diabetes. After 6 h the compound significantly decreased the serum fatty acid desaturation index (−84.4 ± 15.9%) compared to

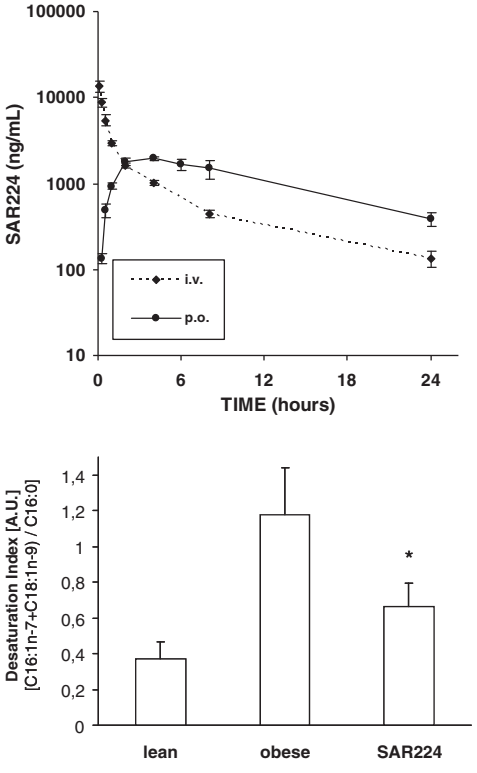


Figure 3. Upper: Pharmacokinetic parameters of **SAR224** following an intravenous bolus administration of 5 mg/kg **SAR224** and following a single oral dose of 30 mg/kg **SAR224** to male obese ZDF rats. Results are means ± SD (n = 3). Lower: Decreased serum fatty acid desaturation indices (−84.4 ± 15.9%) by treatment of male obese ZDF rats with 30 mg/kg **SAR224**. Results are means ± SEM (n = 8) and $^*p$ <0.05 versus the vehicle-treated, obese controls.

vehicle in the obese animals (Fig. 3, lower), thus providing evidence for SCD1 inhibition in vivo by **SAR224**.

In conclusion, we have described the identification, design and structure–activity relationships of a novel series of potent SCD1 inhibitors based on a benzimidazole scaffold. This series was developed following promising results from a ligand-based virtual screen. Major parts of the scaffold were then appropriately substituted to arrive at compounds having high affinity as SCD1 inhibitors and favorable physicochemical and ADMET properties.

Finally **SAR224** which showed the most promising in vitro properties was characterized by in vivo PK and pharmacology studies, which revealed strong evidence for in vivo SCD1 inhibition by this molecule with suitable oral bioavailability and half-life. Hence **SAR224** constitutes a promising starting point for further investigation of SCD1 inhibitors as potential treatments of diabetes and related diseases.

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