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Novel, potent, selective, and metabolically stable stearoyl-CoA desaturase (SCD) inhibitors

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ABSTRACT

We identified a series of structurally novel SCD (Δ9 desaturase) inhibitors via high-throughput screening and follow-up SAR studies. Modification of the central bicyclic scaffold has proven key to our potency optimization effort. The most potent analog (**8g**) had IC_{50} value of 50 pM in a HEPG2 SCD assay and has been shown to be metabolically stable and selective against Δ5 and Δ6 desaturases.

Stearoyl-CoA desaturases (SCD's), also known as Δ9 fatty acid desaturases are microsomal enzymes that utilize CoA conjugates of saturated long-chain fatty acids (primarily, stearic acid, and palmitic acid) to introduce a cis-double bond in the C-9 and C-10 position. The reaction requires molecular O_2 and NADH and generates H_2O in the process.[1,2] Two isoforms (SCD1 and SCD5, also known as SCD2) have been identified in humans. SCD1 is primarily found in liver, adipose and skeletal muscle and is well characterized[3] compared to SCD2 which is found primarily in the brain.[4] Deletion, mutation or inhibition of SCD1 in mice and rats results in decreased hepatic triglycerides,[5–9] resistance to weight gain and improvements in insulin sensitivity and glucose uptake. Thus, SCD inhibition may offer a new treatment for obesity, insulin resistance, and diabetes.[10–12]

The development of isoform-selective compounds may be challenging due to the high homology of SCD1 and SCD2. In addition, SCD1 inhibition in peripheral tissues like skin and pancreas may lead to side-effects.[7,13] In light of these observations, the development of tissue selective, non-brain penetrating compounds may be more desirable. As a result the compounds described in this letter were not designed to be SCD1 isoform selective, but rather to be tested later for appropriate in vivo pharmacokinetics and pharmacodynamics.

Δ9 Desaturases are localized to the endoplasmic reticulum and complexed with cytochrome *b5* and cytochrome *b5* reductase. This feature is shared with Δ5 and Δ6 desaturases. Therefore, it is critical to focus the screening effort on small-molecule inhibitors that act directly on SCD enzyme itself, and not on cytochrome *b5* or cytochrome *b5* reductase. We chose to counterscreen lead molecules against Δ5 and Δ6 desaturases as a part of our discovery paradigm.

Sterculic acid (**1**, Fig. 1)[14] is a naturally occurring SCD inhibitor. A large number of small-molecule SCD inhibitors have been published to date (e.g., **2**–**4**).[15–17] The striking similarities among many of reported structures underscore the narrow pharmacophoric space of SCD inhibitors and the difficulty in generating a unique IP position when using the literature leads.

We were keen on pursuing an independent approach to discovering new structural series. Using a rat microsomal SCD assay derived from the literature,[14] we performed a screen of approximately 5.2 million unique and proprietary compounds. Initial hits were

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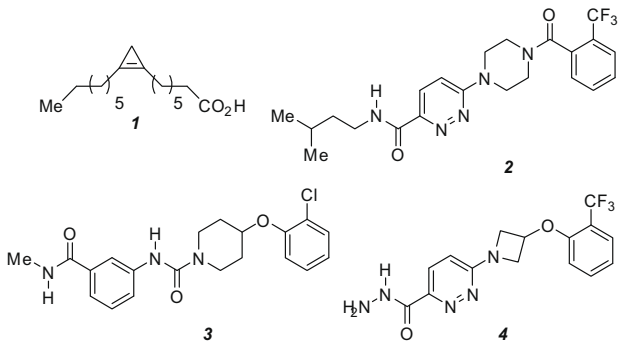


Figure 1. Structures of reported SCD Inhibitors.

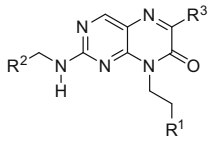
followed up using a cell-based HEPG2 SCD assay. We were not surprised to see differences in IC_{50} values between rat microsomal and human HEPG2 assays because of differences in species and the potential for efficacious compounds in the microsomal assay to not cross the cell membrane or conversely accumulate in the cell as a result of active transport. We set out to find the compounds with high inhibitory potency in both assays. We selected hit compounds **5a** and **5b** (Table 1, IC_{50} 210 nM/410 nM and 2.8 μM/1.67 μM in rat microsomal/HEPG2 SCD assays) for SAR follow-up. Synthesis of compounds in series **5** was carried out in 4 steps, starting with commercially available 2,4-dichloro-5-nitropyrimidine (**9**; X, Y = N; Scheme 1; Method A). Initially, amination of **9** (X, Y = N) using a primary amine [$R^1(CH_2)_2$–NH_2] at room temperature allows regioselective nucleophilic displacement to be conducted at C-4 based on the increased reactivity of the 4-chloro position. Further amination with R^2CH_2–NH_2 was conducted at 60 °C overnight to provide **10**.[18] Reduction of the nitro group was achieved by either a sodium dithionate method or with Raney Nickel.[19,20] Final reaction with an α-ketoester, followed by cyclization to the pteridinone incorporated the R^3 substituent.[21]

Through expansion of the SAR around series **5** (Table 1) we have found that the R^1 substituent must contain either an amide (preferred) or a sulfonamide group separated from the scaffold by two methylene units. A number of substituted benzylamines are tolerated at R^2 position, including 3,4-dichlorobenzyl and 3-(trifluoromethyl)benzyl, but the NH is mandatory. Replacement of the NH with O, S, and *N*-methyl all resulted in inactive compounds. Finally, we screened a number of R^3 substituents, relying mostly on commercially available aryl-substituted ketoesters. We found that the 3-pyridyl (**5k**, **l**), 4-chlorophenyl (**5n**), and 4-methylphenyl (**5o**) were the only substituents that, in some cases, match the potency of the 4-methoxyphenyl substituent. The majority of analogues of **5** did not present a significant improvement over the initial hit **5a**. In the HEPG2 SCD assay, two compounds (**5j** and **5o**) showed surprisingly high potency. Both **5j** and **5o** possess the combination of a 3-(trifluoromethyl)phenyl group in the R^2 position and a $CONH_2$ group ('reverse amide') in the R^1 position.

Next, we turned our attention to the scaffold itself. We decided to keep the rather unique pyrazin-2(1*H*)-one ring B of the pteridinone system intact and replace the pyrimidine ring A with the 5-aza isomer of the pyridine ring, resulting in the alternative [6,6]-bicyclic system **6** (Fig. 2). The synthesis of series **6** compounds was similar to series **5**, employing 2,6-dichloro-3-nitropyridine (**9**; X = CH, Y = N) as a starting material (Scheme 1; Method A). At first, we kept the acetamide and 4-methoxyphenyl moieties in positions R^1 and R^3, respectively, and focused on exploring the effect of the R^2 substituent on inhibitory potency in the rat microsomal assay. The most interesting compounds were followed up on in the HEPG2 SCD assay to confirm activity (Table 2).

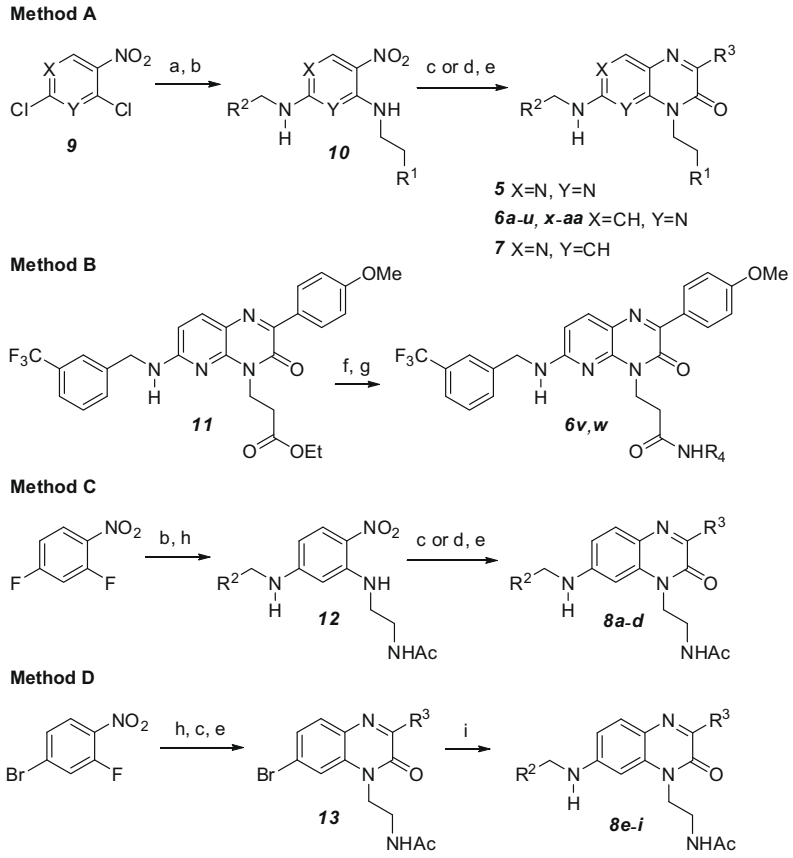
As a general observation, series **6** presented an improvement over series **5** for potency of SCD inhibition in both microsomal and HEPG2 assays. Compound **6a** displayed IC_{50} values of 220 nM and 81 nM in the microsomal and HEPG2 SCD assays, respectively. A number of R_2 substituents have been tested and resulted in compounds with superior activity relative to **5a** in the HEPG2 SCD assay including 3-chloro-4-fluorophenyl (**6e**, IC_{50} 47 nM), 3-(trifluoromethyl)phenyl (**6f**, 47 nM), 3,5-bis-(trifluoromethyl)phenyl (**6i**, IC_{50} 51 nM), and 4-fluoro-3-(trifluoromethyl)phenyl (**6j**, IC_{50} 16 nM). A clear trend points towards the preference for lipophilic, halogenated substituents in the 3- and 4-positions on the aromatic ring. Of those, the 3-position has a greater tolerance for steric bulk and greater overall impact on potency in both the microsomal and

Table 1
Structure–activity relationships in pteridinone series **5**



	Substituents			Δ9 IC_{50}, nM	
	R^1	R^2	R^3	Rat Mic. SCD	HEPG2 SCD
5a	NHAc	3,4-Dichlorophenyl	4-Methoxyphenyl	210	410
5b	$NHSO_2Me$	3,4-Dichlorophenyl	4-Methoxyphenyl	2800	1670
5c	NHCOEt	3,4-Dichlorophenyl	4-Methoxyphenyl	2800	n.d.[a]
5d	NHCOPh	3,4-Dichlorophenyl	4-Methoxyphenyl	560	>30,000
5e	NHCO-3-Thienyl	3,4-Dichlorophenyl	4-Methoxyphenyl	470	4000
5f	$CONH_2$	3,4-Dichlorophenyl	4-Methoxyphenyl	177	140
5g	NHAc	3-Chlorophenyl	4-Methoxyphenyl	1300	4600
5h	NHAc	3-Fluoro-4-chlorophenyl	4-Methoxyphenyl	900	n.d.
5i	NHAc	4-Fluoro-3-chlorophenyl	4-Methoxyphenyl	750	n.d.
5j	$CONH_2$	3-(Trifluoromethyl) phenyl	4-Methoxyphenyl	145	5.6
5k	NHAc	3,4-Dichlorophenyl	3-Pyridyl	270	250
5l	$CONH_2$	3,4-Dichlorophenyl	3-Pyridyl	513	36
5m	$CONH_2$	3-(Trifluoromethyl) phenyl	3-Pyridyl	1890	92
5n	$CONH_2$	3-(Trifluoromethyl) phenyl	4-Chlorophenyl	330	n.d.
5o	$CONH_2$	3-(Trifluoromethyl) phenyl	4-Methylphenyl	134	9.6

[A] Not determined.



Scheme 1. Reagents and conditions: (a) amine, $(i\text{-Pr})_2$NEt, THF, rt, 24 h; (b) amine, $(i\text{-Pr})_2$NEt, THF, 60 °C, 24 h; (c) $NH_2NH_2{\cdot}H_2O$, Raney Ni, MeOH, 60 °C, 24 h; (d) $Na_2S_2O_4$, Na_2CO_3, dioxane/water 1:1, 100 °C, 24 h; (e) ketoester, EtOH, 2% v/v AcOH, 80 °C, 24 h; (f) $LiOH{\cdot}H_2O$, H_2O/THF/MeOH, rt, 24 h; (g) amine·HCl, EDC·HCl, HOBt, $(i\text{-Pr})_2$NEt, $CHCl_3$, rt, 24 h; (h) amine, $(i\text{-Pr})_2$NEt, acetonitrile, reflux, 24 h; (i) amine, $Pd_2(dba)_3$, BINAP, NaO*t*-Bu, toluene, microwave, 120 °C, 10 min.

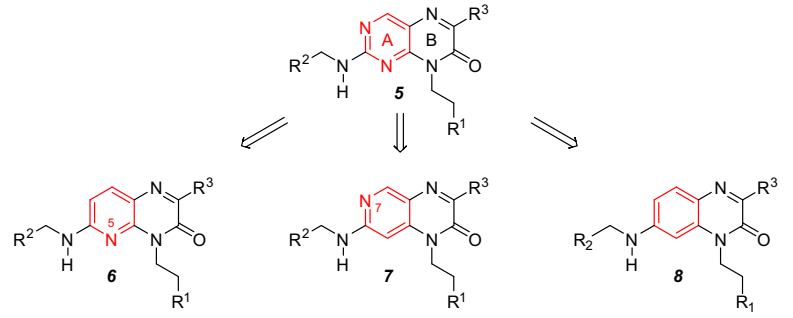


Figure 2. Structures of reported SCD inhibitors.

the HEPG2 SCD assays. For example, 3-(trifluoromethyl)phenyl analogue **6f** is over 50 times more potent than 4-(trifluoromethyl)phenyl analogue (**6h**, IC_{50} 2.5 μM) in the HEPG2 SCD assay. One interesting exception is the 4-chlorophenyl substituent. Compound **6b** turned out to be the most potent analogue in microsomal assay among the series **6** compounds (IC_{50} 7.8 nM); however, its HEPG2 activity was somewhat more moderate (IC_{50} 110 nM).

Next, while staying within scaffold **6**, we switched to the reverse amide group in the R^1 position and explored some limited SAR (Table 3). Compounds **6t** and **6u** were synthesized by the previously detailed procedure (R_4 = H; Scheme 1; Method A), using β-alanine amide hydrochloride in the first step. However, for **6v** and **6w**, the analogous substituted β-alanine amides were not available. We modified our synthetic approach to utilize β-alanine ethyl ester hydrochloride instead, and obtained compound **11** (Scheme 1; Method B).

The ethyl ester in **11** was hydrolyzed and the resulting carboxylic acid was coupled with methylamine and *O*-methylhydroxylamine to obtain compounds **6v** (R^4 = Me) and **6w** (R^4 = OMe), respectively.

We have found that the smallest R^4 substituent, hydrogen, is preferred (**6t** and **u**). As observed within series **5**, the most potent analogue in the HEPG2 SCD assay (**6u**) also possessed a combination of a 3-(trifluoromethyl)phenyl group in the R^2 position in conjunction with the reverse amide in the R^1 position.

In the course of our SAR studies in Series **5**, the 4-methoxyphenyl substituent at the R^3 position resulted in the highest number of active compounds. Another substituent of interest was 3-

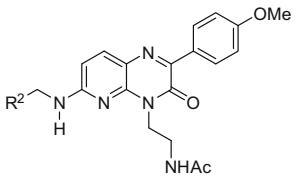
pyridyl. We were interested in the effect the 3-pyridyl substituent may have on potency when combined with scaffold **6** (Table 4). We found that compound **6x** was the most potent (IC_{50} 127 nM and 15 nM in the microsomal and HEPG2 SCD assays, respectively) among all 3-pyridyl analogues.

Next, we turned our attention to the isomeric (7-aza) pyridine core structure **7** (Fig. 2). Compounds of series **7** were obtained from 2,4-dichloro-5-nitropyridine (**9**; X = N, Y = CH; Scheme 1; Method A) which was prepared as described in the literature.[22] Compounds **7a** and **7b** (Table 5) are direct analogues of their isomeric counterparts (**6a** and **6x**, respectively). Based on this direct comparison the heterocyclic core **7** does not present any advantages over **6** in terms of potency of SCD inhibition.

Finally, we investigated the effect of the core structure with fused benzene as Ring A (**8**, Fig. 2). Compounds of series **8** were prepared by two different methods (Scheme 1; Methods C and D). Method C is very similar to method A, except 2,4-difluoro-1-nitrobenzene is used as a starting material and fluoride serves as a leaving group instead of chloride. Method D is centered on coupling between bromide **13** and amines containing the R^2-group under Buchwald conditions.[23] Series **8** (Table 6) provided analogues with very high potency for SCD inhibition. For example, compound **8g** displayed 0.6 nM potency of SCD inhibition in the microsomal assay and 50 pM in the HEPG2 SCD assay—by far the most potent SCD inhibitor reported to date. The higher potency of some compounds in cell-based assay was likely due to either species differences or accumulation of the compound intracellularly.

As previously indicated, we were interested in our compounds' selectivity against other desaturases, specifically Δ5 and Δ6. We determined Δ5 and Δ6 selectivity in microsomal assays[24] for a number of representative compounds from each class, and all compounds tested were found to have IC_{50} values >30 μM, ensuring 100–50,000-fold selectivity windows (Table 7). Another important characteristic essential for drug development is metabolic stability in human and rat liver microsomes. Representative compounds were evaluated in microsomal stability assays and displayed stability of 50% or greater following a 30 min microsomal incubation. This also supported that inhibitory activity results against Δ9 desaturase, a microsomal enzyme, were not affected to any significant extent by microsomal metabolism.

Table 2
Structure–activity relationships in series **6** (amides, **6a**–**s**)



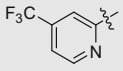
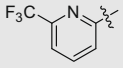
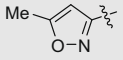
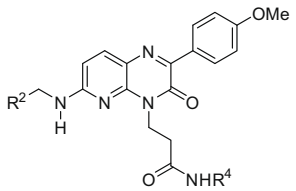
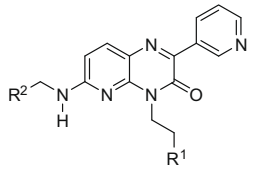
	Substituents	Δ9 assay, IC_{50}, nM	
	R^2	Rat mic.	HEPG2
6a	3,4-Dichlorophenyl	220	81
6b	4-Chlorophenyl	7.8	110
6c	3-Chlorophenyl	376	100
6d	2-Chlorophenyl	549	n.d.
6e	3-Chloro-4-fluorophenyl	466	47
6f	3-(Trifluoromethyl)phenyl	206	47
6g	3-(Trifluoromethoxy)phenyl	260	210
6h	4-(Trifluoromethyl)phenyl	2050	2500
6i	3,5-bis-(Trifluoromethyl)phenyl	217	51
6j	4-Fluoro-3-(trifluoromethyl)phenyl	20	16
6k	2-Fluoro-5-(trifluoromethyl)phenyl	1480	n.d.
6l		330	180
6m		13,790	n.d.
6n		>30,000	n.d.
6o	3-Methylphenyl	380	96
6p	3-Fluorophenyl	17,600	n.d.
6q	phenyl	840	n.d.
6r	3-Methoxyphenyl	760	n.d.
6s	3-Carboxyphenyl	>30,000	n.d.

Table 3
Structure–activity relationships in series **6** (reverse amides, **6t**–**w**)



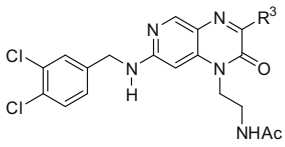
	Substituents		Δ9 assay, IC_{50}, nM	
	R^2	R^4	Rat mic.	HEPG2
6t	3,4-Dichlorophenyl	H	29	16
6u	3-(Trifluoromethyl)phenyl	H	27	2.8
6v	3-(Trifluoromethyl)phenyl	Me	360	120
6w	3-(Trifluoromethyl)phenyl	OMe	930	n.d.

Table 4
Structure–activity relationships in series **6** (pyridines, **6x**–**aa**)



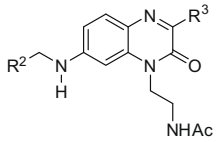
	Substituents		Δ9 assay, IC_{50}, nM	
	R^1	R^2	Rat mic.	HEPG2
6x	NHAc	3,4-Dichlorophenyl	127	15
6y	NHAc	3-Chloro-4-Fluorophenyl	333	13
6z	NHAc	3-(Trifluoromethyl) phenyl	1400	120
6aa	$CONH_2$	3-(Trifluoromethyl) phenyl	30,000	n.d.

Table 5
Structure–activity relationships in series **7**



	Substituents	Δ9 assay, IC_{50}, nM	
	R^3	Rat mic.	HEPG2
7a	4-Methoxyphenyl	190	34
7b	3-Pyridyl	157	21
7c	4-Methylphenyl	343	40

Table 6
Structure–activity relationships in series **8**



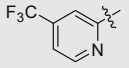
	Substituents		Δ9 assay, IC_{50}, nM	
	R^2	R^3	Rat mic.	HEPG2
8a	3,4-Dichlorophenyl	4-Methoxyphenyl	110	8.6
8b	3-(Trifluoromethyl) phenyl	4-Methoxyphenyl	93	3.3
8c	3-(Trifluoromethyl) phenyl	3-Pyridyl	168	13
8d	3-(Trifluoromethyl) phenyl	4-Ethylphenyl	56	3.2
8e	3-Methylphenyl	4-Methoxyphenyl	18	13
8f	3,4-Dimethylphenyl	4-Methoxyphenyl	26	130
8g	4-Chloro-3-(trifluoro methyl)phenyl	4-Methoxyphenyl	0.6	0.05
8h	4-Fluoro-3-methylphenyl	4-Methoxyphenyl	0.5	3.1
8i		4-Methoxyphenyl	25	6.5

Table 7
Desaturase selectivity and microsomal stability of selected analogues

	Other stearolyl-CoA desaturase activity (Δ9 selectivity)		Liver microsomal stability, % after 30 min	
	Rat mic. Δ5 IC_{50}, μM	Rat mic. Δ6 IC_{50}, μM	Human	Rat
5a	>30 (>120)	>30 (>120)	51	47
6a	>30 (>187)	>30 (>187)	85	72
6t	>30 (>158)	>30 (>158)	94	106
6u	>30 (>857)	>30 (>857)	69	61
6x	>30 (>411)	>30 (>411)	69	49
7a	>30 (>882)	>30 (>882)	97	92
8a	>30 (>272)	>30 (>272)	83	54
8g	>30 (>50,000)	>30 (>50,000)	81	83

In conclusion, we conducted a SAR study of structurally novel bicyclic SCD inhibitors based on pteridinone screening hits **5a** and **5b**. Modifications of the ring A of the bicyclic core from pyrimidine **5** to 5- and 7-isomers of pyridine (**6** and **7**) to benzene **8** had the greatest impact on potency optimization. Preferred substituents were also identified in R^1, R^2, and R^3 positions. Overall, our effort led to the discovery of highly potent (against both human and rat enzymes), selective, metabolically stable, and structurally novel Δ9 desaturase (stearoyl-CoA desaturase, SCD) inhibitors. Work is underway to fully characterize their in vivo pharmacokinetic and pharmacodynamic properties in various animal models.

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