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Discovery of spirocyclic-diamine inhibitors of mammalian acetyl CoA-carboxylase

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ABSTRACT

A novel series of spirocyclic-diamine based, isoform non-selective inhibitors of acetyl-CoA carboxylase (ACC) is described. These spirodiamine derivatives were discovered by design of a library to mimic the structural rigidity and hydrogen-bonding pattern observed in the co-crystal structure of spirochromanone inhibitor **I**. The lead compound **3.5.1** inhibited de novo lipogenesis in rat hepatocytes, with an IC_{50} of 0.30 μM.

Fundamental imbalances in lipid metabolism have been hypothesized to contribute to the pathogenesis of non-alcoholic fatty liver disease (NAFLD), insulin resistance and type 2 diabetes mellitus (T2DM).[1–3] Elevated rates of hepatic de novo lipogenesis (DNL) and suppressed basal fatty acid oxidation are believed to contribute to net ectopic accumulation of lipid species in liver and skeletal muscle.[3] Accumulation of lipid species including diacylglycerol[1,4,5] and ceramides[6] has been postulated to underlie the pathogenesis of insulin resistance. This mechanism is supported by the inverse relationship between insulin sensitivity and both hepatic[7,8] and intramyocellular[9] triglyceride levels observed in rodent models and in humans, and in some (but not all) transgenic rodent studies.[1] Acetyl-CoA carboxylase (ACC) is a critical regulator of lipid metabolism, controlling the switch between lipogenic and oxidative metabolism.[10] ACC catalyzes the ATP-dependent condensation of acetyl-CoA with carbonate to form malonyl-CoA. Malonyl-CoA is an essential substrate for DNL and regulates fatty acid oxidation through allosteric inhibition of carnitine palmitoyltransferase 1.[11] ACC enzyme inhibition suppresses DNL and promotes fatty acid oxidation leading to lower ectopic lipid levels. These changes may also lead to improvements in insulin sensitivity. Suppression of ACC activity in rodents decreases tissue malonyl CoA levels, increases fatty acid oxidation and/or inhibits lipogenesis, and reduces triglyceride accumulation in skeletal muscle and/or liver. These changes improve insulin sensitivity as demonstrated with anti-sense oligonucleotides[12] and some small molecule inhibitors.[13,14] Pharmacologic ACC inhibitors may therefore have utility in the treatment of NAFLD and T2DM;[15] the first human clinical data on a small molecule ACC inhibitor have recently been disclosed.[16]

There are two closely related isoforms of ACC termed ACC1 and ACC2. We sought dual inhibitors because inhibition of both

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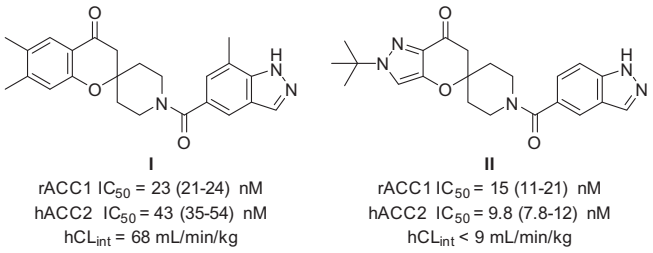


Figure 1. ACC inhibitors **I** and **II**. Rat ACC1 (rACC1) and human ACC2 (hACC2) potencies, geometric mean with 95% confidence intervals reported in parentheses; hCL_{int}: intrinsic clearance in human liver microsomal incubations.

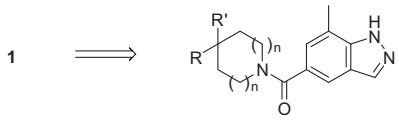


Figure 2. Library design: R or R′ contains a suitable hydrogen bond acceptor.

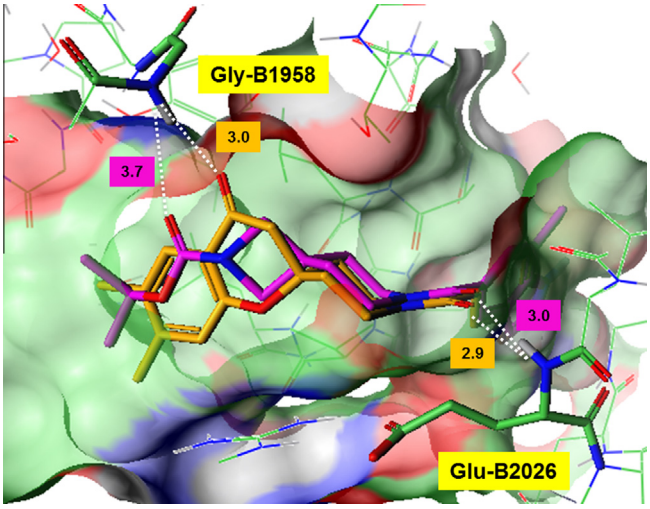


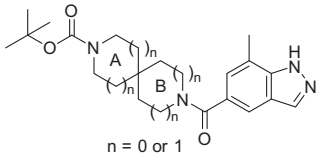
Figure 3. Co-crystal structure of **1.4** (pink) in the CT-domain of ACC, overlaid with the bound conformation of **I** (orange). pdb accession codes: **I**, 5CTB; **1.4**, 5CTC.

isoforms may be important to maximize pharmacological effects on lipid metabolism and efficacy. The spirochromanone[17] (**I**) and spiroketopyrazole[18] (**II**) series of compounds inhibit ACC by binding to the carboxyltransferase (CT) domain, and the potency of these compounds provided attractive starting points for identification of an alternate chemical series of ACC inhibitors (see Fig. 1). In assessing the structures and associated properties of these compounds, the ketone functional group was identified as a potential risk. The possibility of in vivo reduction of the ketone (and possible re-oxidation of the resulting alcohol) was a concern because of the difficulty of predicting the extent of this metabolic pathway in humans. Further, the possible electrophilic reactivity of the ketone was a safety risk that we sought to mitigate. Analysis of the SAR and inspection of co-crystal structures in the spirochromanone and spiroketopyrazole series led to two guiding hypotheses: (a) the two hydrogen bond acceptor functional groups (amide and ketone carbonyls) were important for binding potency, and (b) the structural rigidity imparted by the spirocyclic ring system made significant contributions to binding by decreasing the entropic penalty for properly orienting the hydrogen bond acceptors.

In order to identify an alternate, non-ketonic structural series, the two hypotheses outlined above were coupled to a synthetic strategy that leveraged the diversity of our corporate compound collection in combination with efficient synthetic chemistry. The 5-carboxy-7-methyl-indazole derived amide, which demonstrated high relative contributions to potency and ligand efficiency in the spirochromanones, was selected as an 'anchor' group for design of a library that would couple the corresponding carboxylic acid to amines intended to mimic the spirochromanone scaffold and its ketone hydrogen bond acceptor (Fig. 2). The synthetic chemistry to couple 5-carboxy-7-methyl-indazole to cyclic secondary amines under standard amidation conditions was well established.[18] Cyclic secondary amines with distal hydrogen bonding groups (most commonly, carbonyls such as amides or carbamates) were selected as the amine coupling partners for this library.

Inhibition of rat ACC1 and human ACC2 was assayed as described in the literature.[18] Several hits from the initial library came from a sub-class of compounds derived from *t*-butyl carbamate-capped spirodiamine cores.[19–27] A second iteration of compounds was synthesized to provide the full set of permutations shown in Table 1. Modeling (not shown) into the co-crystal structure of spirochromanone **I** enabled the conclusions that a 4,4-system (**1.6**) was too short to span the necessary distance between the hypothesized H-bonding groups and that the 5,5-core (**1.5**) was too angular to be well-matched to the shape of the binding pocket. However, the similar potencies of the 5,6- and

Table 1
N-t-Butoxycarbonyl-substituted spirodiamine ACC inhibitors



Compd	Ring A	Ring B	*e*Log*D*	rACC1 (μM)	hACC2 (μM)	hCL_{int} (mL/min/kg)
1.1	6	5	2.8	1.0 (0.67–1.6)	2.2 (1.5–3.2)	94
1.2	5	6	3.0	0.51 (0.36–0.73)	1.0 (0.90–1.2)	32
1.3	6	4	2.5	0.81 (0.78, 0.84)[a]	2.4 (0.98–5.7)	19
1.4	4	6	2.6	0.45 (0.38–0.53)	0.80 (0.50–1.3)	<9
1.5	5	5	2.6[b]	11 (7.4, 17)[a]	20 (7.7–51)	ND
1.6	4	4	2.2[b]	>30	>10	ND

rACC1 and hACC2 potencies are generally the geometric mean of at least 3 replicates (95% confidence interval in parentheses).
[a] For $n = 2$ replicates, the individual measurements are reported in parentheses.
[b] Calculated *e*Log*D*.