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Discovery of small molecule isozyme non-specific inhibitors of mammalian acetyl-CoA carboxylase 1 and 2

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ABSTRACT

Screening Pfizer's compound library resulted in the identification of weak acetyl-CoA carboxylase inhibitors, from which were obtained rACC1 CT-domain co-crystal structures. Utilizing HTS hits and structure-based drug discovery, a more rigid inhibitor was designed and led to the discovery of sub-micromolar, spirochromanone non-specific ACC inhibitors. Low nanomolar, non-specific ACC-isozyme inhibitors that exhibited good rat pharmacokinetics were obtained from this chemotype.

Type-2 diabetes mellitus (T2DM) has reached epidemic proportions and threatens to become a global health scourge, currently accounting for an estimated 5% of global deaths.[1] Furthermore, the World Health Organization (WHO) estimates that diabetes-related deaths 'are likely to increase by more than 50% in the next 10 years without urgent action'.[1] A co-morbidity associated with diabetes is obesity. Obesity related co-morbidities includes hypertension, dyslipidemia, coronary heart disease, stroke, some forms of cancer, musculoskeletal disorders and other cardiovascular diseases that further accelerate the morbidity and mortality associated with obesity and diabetes. Global 2005 estimates from WHO indicate that 1.6 billion adults over the age of 15 were overweight, with at least 400 million adults being obese. The fact that at least 20 million children under 5 years old are categorized as overweight foretells future health problems since 'childhood obesity is associated with a higher chance of premature death and disability in adulthood'.[2] Medicaments are now being prescribed to treat childhood obesity, as evidenced by the use of cholesterol reducing medications in this population group.[3] Even though T2DM and obesity can be deterred through diet modification and increased physical exercise, pharmacologic interventions continue to be sought to treat these diseases.

A drug agent that would be expected to impact T2DM and obesity would have the potential to positively impact health outcomes for diabetics and the obese. The inhibition of acetyl-CoA carboxylase (ACC) is under investigation since modulation of its activity poses the potential to modulate diabetes and obesity.[4] ACC is one of the enzymes responsible for modulating the rate of long chain fatty acid biosynthesis and the rate of mitochondrial fatty acid oxidation. ACC is a biotin-dependent heterodimeric protein, composed of carboxyltransferase (CT), biotin carboxy carrier protein (BCCP), and biotin carboxylase (BC) domains, whose purpose is to synthesize malonyl-CoA (m-CoA) from acetyl-CoA in an ATP-dependent reaction via the fixation of bicarbonate.[5] The synthesis of m-CoA is a two step process wherein the first half-reaction occurs in the BC-domain and involves the ATP-dependent reaction between bicarbonate ion and enzyme-bound biotin to afford a

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biotin-carboxylate complex. The newly formed biotin-carboxylate complex enters the CT-domain via a narrow channel between the CT- and BC-domains, where carbon dioxide is transferred from biotin carboxylate to acetyl-CoA to form m-CoA. Malonyl-CoA is then utilized by other enzymes as the substrate for de novo fatty acid synthesis and fatty acid chain elongation as well as being used as an allosteric inhibitor of carnitine palmitoyltransferase (CPT1), thereby playing a role in modulating fatty acid oxidation.

Two isoforms of mammalian ACC are known, ACC1 and ACC2 (also known as ACCα and ACCβ, respectively). ACC1 is a cytosolic enzyme that produces m-CoA that is believed to utilized in de novo fatty acid synthesis and fatty acid chain elongation while ACC2 is associated with the mitochondrial outer membrane where it may play a predominate role in producing m-CoA that functions to regulate fatty acid oxidation via allosteric inhibition of CPT1. ACC1 is found primarily in lipogenic tissues such as the liver and adipose tissue whereas ACC2 is the predominate form found in oxidative tissues (skeletal muscle and heart) where it plays a role in modulating energy expenditure. Therefore, an ACC1/2 isozyme nonselective inhibitor would be predicted to reduce fatty acid synthesis in liver and adipose tissue while at the same time increasing fatty acid oxidation in the liver and muscle tissues resulting in increased energy expenditure, decreased whole body adiposity, concomitant decreased weight gain and/or weight loss, and improved insulin sensitivity.

Screening of the Pfizer compound file and triage of the resulting hits resulted in the identification of the micromolar screening hit **1** (rACC1 IC_{50} = 8910 nM, Fig. 1). Modeling of **1** suggested that it was binding to the same CT-domain binding channel as the historic series of ACC inhibitors, characterized by **CP-640186**.[6,7] The hypothesis was made that if compound **1** had a similar binding pose as **CP-640186**, then the corresponding anthracene and 2-phenylquinoline amide derivatives **2** and **3** would be more potent ACC1 inhibitors since these groups led to improved potency in the **CP-640186** series of ACC inhibitors. This was indeed the case as evidenced by rACC1 IC_{50} = 325 and 842 nM for **2** and **3**, respectively. CT-domain co-crystal structures of these compounds confirmed the proposed binding mode.[8] The crystal structure of compound **2** (in blue) is shown in Figure 2 along with an overlay of **CP-640186** (in yellow, extracted from Tong's crystal structure),[7] showing that both compounds are capable of binding to the same channel within the CT-domain. The crystal structures indicate that the anthracene rings in **CP-640186** and **2** occupy a similar region of space, the morpholinyl-amide of **CP-640186** is in approximately the same region of space as the methylquinoline and the H-bond between the amide carbonyl and Glu-B2026 is conserved between both compounds.

Owing to the sub-optimal physicochemical properties of the arylquinoline and anthracene amides, the chemistry team focused

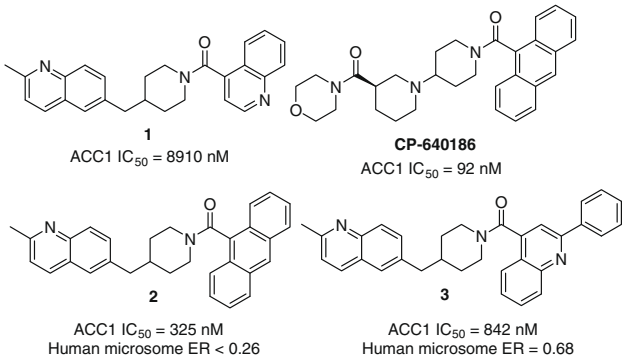


Figure 1. Structure of HTS hit **1**, **CP-640186** and select analogs.

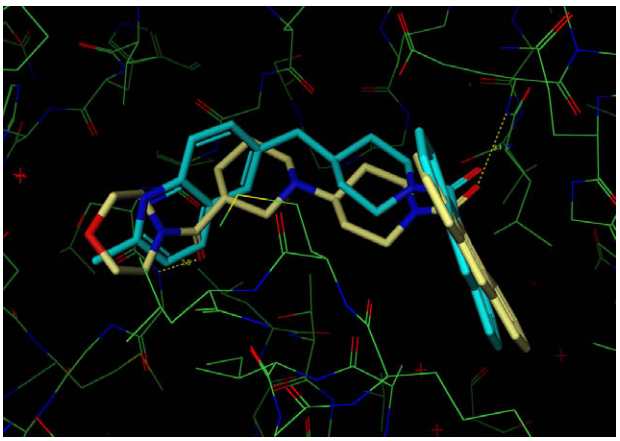


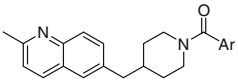
Figure 2. CT-domain co-crystal structure of **2** (blue) and **CP-640186** (yellow).

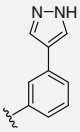
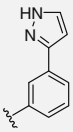
on improving inhibitory potency without reverting to these functional groups. Toward that end, a carboxylic acid scan was conducted on the methylquinoline template and multiple non-arylquinoline derivatives with rACC1 IC_{50} < 5 μM were identified (Table 1). Compound **4** was one of the most ligand efficient (LE) inhibitors identified, with a LE of 0.26 and rACC1 IC_{50} = 3.38 μM.[9] Other compounds found during the scan were *m*-substituted aryl derivatives, such as pyrazoles **5** and **6**.

Compounds **4** and **6** were submitted for rat PK and the data are summarized in Table 2. The team was encouraged by modest oral bioavailability (fraction absorbed >100%) and half-life achieved with the methylquinoline-indazole **4**. However, additional SAR on the quinoline template failed to afford needed increases in potency and it became apparent that the current template was unlikely to afford sub-micromolar potency without resorting to arylquinoline carboxylic acids.

The inability to advance the quinoline-series SAR without resorting to undesirable carboxylic acids resulted in the need to identify an alternate chemotype. The yeast CT-domain co-crystal structures of compounds **2** and **3** were subsequently used as the basis for structure-based drug design. Crystal structure of derivatives **2** and **3** showed a single H-bond interaction between the protein and ligand, namely a hydrogen-bond between the amide

Table 1
Selected data from carboxylic acid scan on methylquinoline template



Compd	Ar	rACC1 IC_{50}, nM[10]	rACC1 LE[a]
4		3380	0.26
5		1270	0.26
6		3010	0.24

[a] LE is ligand efficiency (LE = −1.4 log IC_{50}/number of heavy atoms).