## Synthesis and Structure–Activity Relationships of *N*-{3-[2-(4-Alkoxyphenoxy)thiazol-5-yl]-1methylprop-2-ynyl}carboxy Derivatives as Selective Acetyl-CoA Carboxylase 2 Inhibitors

Yu Gui Gu,\* Moshe Weitzberg, Richard F. Clark, Xiangdong Xu, Qun Li, Tianyuan Zhang, T. Matthew Hansen, Gang Liu, Zhili Xin, Xiaojun Wang, Rongqi Wang, Teresa McNally, Heidi Camp, Bruce A. Beutel, and Hing L. Sham

Metabolic Disease Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 200 Abbott Park Road, Abbott Park, Illinois 60064

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**Abstract:** A structurally novel acetyl-CoA carboxylase (ACC) inhibitor is identified from high-throughput screening. A preliminary structure– activity relationship study led to the discovery of potent dual ACC1/ ACC2 and ACC2 selective inhibitors against human recombinant ACC1 and ACC2. Selective ACC2 inhibitors exhibited IC<sub>50</sub> < 20 nM and >1000-fold selectivity against ACC1. (*S*)-Enantiomer **9p** exhibited high ACC2 activity and lowered muscle malonyl-CoA dose-dependently in acute rodent studies, whereas (*R*)-enantiomer **90** was weak and had no effect on the malonyl-CoA level.

The incidence of type 2 diabetes has dramatically increased over the past decade. There is ample evidence to support a strong correlation between insulin resistance and the development of type 2 diabetes mellitus. At the cellular level, an increase in ectopic fat storage in nonadipose tissues such as muscle, liver, and pancreas has been implicated as a strong predictor of the development of insulin resistance and type 2 diabetes.<sup>1,2</sup> Although it is unclear how increased intracellular lipid content exacerbates whole-body insulin sensitivity, it has been suggested that increased levels of long-chain fatty acyl-CoAs, ceramide, or diacylglycerol, whose contents are proportional to the accumulation of intramyocellular triglyceride, antagonize the metabolic actions of insulin, reduce muscle glucose uptake, and inhibit hepatic glucose production.<sup>2,3</sup>

Acetyl-CoA carboxylase<sup>4</sup> (ACC) catalyzes the biotin-dependent carboxylation of acetyl-CoA to form malonyl-CoA<sup>5,6</sup> (mCoA), a key intermediate metabolite that regulates the rate of fatty acid metabolism. mCoA is a known substrate for fatty acid synthase for de novo lipogenesis and also an allosteric inhibitor of carnitine palmitoyltransferase 1, a mitochondrial outer membrane protein that shuttles long-chain fatty acyl-CoAs into the mitochondria for oxidation.<sup>7</sup> Therefore, ACC inhibition is expected to lower mCoA levels, resulting in reduced fatty acid synthesis, increased fatty acid oxidation, and consequently improved insulin sensitivity. In rodents and humans, there are two isoforms of ACC encoded by distinct genes. ACC1, a 265 kDa cytosolic protein, is highly expressed in lipogenic tissues (liver and adipose), whereas the 280 kDa ACC2 isoform is primarily expressed in oxidative tissues (muscle, heart, and liver).<sup>8,9</sup> Recently, there has been increasing interest in the discovery of ACC inhibitors for the treatment of metabolic syndrome, obesity, and type 2 diabetes.<sup>10</sup> Harwood and coworkers reported a class of potent and nonselective inhibitors exemplified by 1 (CP-640186, Figure 1).<sup>11</sup> Compound 1 was



Figure 1. Structures of ACC inhibitors.

reported to increase fatty acid oxidation in mouse muscle cells C2C12 and in rat muscle strips ex vivo. It also acutely lowered mCoA levels in rat liver and muscles and increased whole-body fatty acid oxidation. Thus far, the most potent ACC inhibitor reported is the natural product soraphen A (Figure 1),<sup>12</sup> which is also a nonselective ACC inhibitor with single-digit-nanomolar potency. To our knowledge, there have been no isoformselective ACC inhibitors reported thus far. Although a nonselective ACC inhibitor may be beneficial in maximizing the wholebody fatty acid metabolism by simultaneously inhibiting the fatty acid synthesis in lipogenic tissues and increasing fatty acid oxidation in oxidative tissues,13 genetic studies have demonstrated that ACC1 homozygous knockout mice are embryonically lethal and the safety of chronic inhibition of ACC1 is unknown.<sup>14</sup> On the other hand, ACC2 homozygous knockout mice are healthy and fertile and exhibit a favorable metabolic phenotype of increased fatty acid oxidation, increased thermogenesis, reduced hepatic triglyceride content, and decreased body weight despite increased food intake.<sup>15</sup> In addition, ACC2<sup>-/</sup> mice are resistant to high-fat diet-induced obesity and insulin resistance and demonstrate increased fatty acid and glucose oxidation in adipose tissue. ACC2 is therefore an attractive target for the treatment of obesity-induced type 2 diabetes.<sup>16,17</sup> Here, we report the discovery of a novel class of ACC2 selective inhibitors.

Compound 3 (A-80040, Figure 1), an initial high-throughput screening (HTS) hit from our drug sample room, showed an IC<sub>50</sub> of 80 nM against hACC2 and an IC<sub>50</sub> of 1.0 µM against hACC1 enzyme. This compound originated from our internal 5-lipoxygenase inhibitor program several years ago. The hydroxyurea moiety in 3, while essential for 5-lipoxygenase inhibitory activity,<sup>18</sup> was thought to be a principal cause of the poor pharmacokinetic and toxicity properties associated with the molecule. An initial structure-activity relationship (SAR) study revealed that the hydroxyurea group is not required for ACC inhibitory activity. Urea (9a) and acetamide (9b) (Table 1) replacements for the hydroxyurea resulted in improved ACC2 potency profiles relative to 3. In addition, while the isoform selectivity of 9b is comparable to that of HTS hit 3, 9a showed >1000-fold ACC2 selectivity. These encouraging initial findings led us to focus on this series for lead optimization aimed at identifying potent and selective ACC2 inhibitors.

A general synthesis for *N*-[3-(2-phenoxythiazol-5-yl)-1methylprop-2-ynyl]carboxy derivatives **9** is shown in Scheme 1. The various para-substituted phenols **4** (X = CH, Y = O) employed in Scheme 1 are commercially available or were synthesized via simple chemical transformations. Selective displacement of 2,5-dibromothiazole **5** with **4** in the presence

<sup>\*</sup> To whom correspondence should be addressed. Phone: (847) 937-4792. Fax: (847) 938-3403. E-mail: yu-gui.y.gu@abbott.com.

 Table 1. ACC Inhibitory Activity<sup>a</sup>

#	Structure	hACC1 IC <sub>50</sub> (μM) ± SEM	hACC2 IC <sub>50</sub> (μΜ) ± SEM	
1		0.41 ± 0.06	0.038 ± 0.008	
9a	$ ( )_{O} ( )^{O} ( )_{N}^{S} = ( NH)_{O} ( NH)_{N}^{N} $	>30	0.026 ± 0.002	
9b		0.26 ± 0.06	0.011 ± 0.003	
9c		>30	0.019 ± 0.002	
9d	$\texttt{L}_{S} \textcircled{O}^{O} \textcircled{N}^{S} \underset{O}{\overset{N}{\longrightarrow}} \overbrace{O}^{N} \underset{O}{\overset{N}{\longleftarrow}} $	0.37 ± 0.06	0.055 ± 0.025	
9e		>30	0.15 ± 0.02	
9f		1.25 ± 0.27	>30	
9g		0.39 ± 0.26	0.015 ± 0.003	
9h	$ \downarrow_{0} \swarrow^{S} \overset{S}{\underset{N-}{\longrightarrow}} \overset{S}{\underset{0}{\underset{0}{{\underset{0}{{\underset{0}{}{\underset{0}{0$	>30	0.069 ± 0.007	
9i		>30	1.73 ± 0.48	
<del>9</del> j		>30	0.84 ± 0.006	
9k		>30	0.60 ± 0.10	
91	$ ( )_{0} ( )^{0} ( )^{S} =  ( NH_{2} ) $	>30	2.42 ± 0.13	
9m		>30	0.030 ± 0.005	
9n		>30	0.096 ± 0.013	
90		>30	1.51 ± 0.22	
9p		>30	0.038 ± 0.006	
10		>30	>30	
12		0.029 ± 0.003	0.006 ± 0.001	

<sup>a</sup> The IC<sub>50</sub> data are an average of at least three measurements.

of potassium carbonate at an elevated temperature produced 2-phenoxy-5-bromothiazoles **6** (X = CH, Y = O). Sonogashira coupling<sup>19</sup> of **6** with phthalimide-protected propargylamine **7**, which was prepared from the corresponding alcohol via a Mitsunobu<sup>20</sup> reaction with phthalimide, gave rise to **8** (X = CH, Y = O). Removal of the phthalimide protecting group followed by derivatization of the resulting primary amine provided **9** (X = CH, Y = O).

Similarly, **9g** and **9h** were synthesized starting with 6-isopropoxypyridin-3-ol and 4-isopropoxybenzenethiol, respectively, following the reaction sequence in Scheme 1. Compound **10** was prepared by replacing **5** with 2,4-dibromothiazole according to Scheme 1. The Ullmann coupling reaction of 4-isopropoxyphenol with 1,4-dibromobenzene using Evans' conditions<sup>21</sup> provided biphenyl ether **11**, which was then converted to **12** by Scheme 1<sup>a</sup>



<sup>*a*</sup> Reagents and conditions: (a)  $K_2CO_3$  (1.2 equiv), DMF, 10 min at 180 °C in microwave reactor or 4 h heating at 135 °C, 50–75%; (b) Pd(Ph<sub>3</sub>P)<sub>2</sub>Cl<sub>2</sub> (5% equiv), CuI (2% equiv), Et<sub>3</sub>N (5 equiv), THF, reflux, 3 h, 60–80%; (c) NH<sub>2</sub>NH<sub>2</sub> (10 equiv), CH<sub>2</sub>Cl<sub>2</sub>/EtOH (10:1), reflux, 3 h; (d) Ac<sub>2</sub>O (3 equiv) (or Cl<sub>3</sub>CCON=C=O for **9a**, MeN=C=O for **9m**, MeOCOCl for **9n**-p), Et<sub>3</sub>N (10 equiv), room temp, 3 h, 35–70% (two steps).

following steps b-d in Scheme 1. The enantiomerically pure **90** and **9p** were synthesized by starting with chiral 3-butyn-2ol. Reaction of (*R*)- or (*S*)-3-butyn-2-ol with phthalimide under Mitsunobu conditions produced the corresponding (*S*)- or (*R*)enantiomers **7**, respectively. The reaction proceeded with complete inversion of the chiral center, and the final products were obtained with >98.5% enantiomeric excess and high yield. The two enantiomers have distinct retention times under chiral HPLC conditions, allowing the determination of enantiomeric excess.

Recombinant human ACC1 and ACC2, expressed in HEK293 and baculovirus/Sf9 systems, respectively, were utilized for the measurement of ACC activity. To increase the expression and solubility of ACC2 protein, the N-terminal transmembrane domain (1–275 aa's of ACC2) was replaced with the corresponding ACC1 sequence (1–133 aa's). The enzymatic assay measures ACC-mediated incorporation of [<sup>14</sup>C]CO<sub>2</sub> into malonyl-CoA. Compound **1** was reported as a dual inhibitor against rat ACC1 and ACC2 with virtually equal potency (ACC1 IC<sub>50</sub> = 53 nM and ACC2 IC<sub>50</sub> = 61 nM).<sup>22</sup> Under our assay conditions, it exhibited similar potency against recombinant human ACC2 with IC<sub>50</sub> = 38 nM. The activity against human ACC1 (IC<sub>50</sub> = 410 nM), however, was significantly weaker (Table 1).

SAR studies were carried out by systematically varying the different parts of the molecule, and the results are summarized in Table 1. In general, an ether or thioether linker on the left side of the molecule is optimal for high ACC2 potency (9a-d vs 9e-f). A large lipophilic group on the left side of the molecule appears to increase ACC1 potency (9b,d vs 9c,e). It is interesting that 9f is the only ACC1-selective compound identified, suggesting that the H-bonding acceptor ability of ether or thioether linkers may play an important role in ACC2 inhibitory activity for this class of compounds. Replacement of the phenyl group with a pyridine had little effect on ACC2 activity but reduced ACC2 selectivity (9c vs 9g). The linkage point of the thiazole ring seems to be critical for ACC2 potency. While 9c is a potent and selective ACC2 inhibitor, regioisomer

Table 2. Pharmacokinetic Profile of 9na

species	dose (mg kg <sup>-1</sup> )	F(%)	$V_{\rm ss}$ (L kg <sup>-1</sup> )	$Cl_p  (L  h^{-1}  kg^{-1})$	oral $t_{1/2}$ (h)	oral AUC ( $\mu$ g h mL <sup>-1</sup> )	$C_{\rm max}$ (µg mL <sup>-1</sup> )	$T_{\rm max}$ (h)
rat (n = 3)	5.0	80.4	5.0	0.20	>12	18.9	0.90	2.0

<sup>a</sup> The vehicle used for pharmacokinetic study: 10% DMSO in PEG-400.

10 is inactive against both ACC1 and ACC2. This dramatic activity difference is difficult to understand, given the fact that replacement of thiazole with a para-substituted phenyl resulted in a potent dual inhibitor (12). A methyl group in the propargyl position is optimal for ACC2 activity. Removing this methyl group or replacing it with a larger substituent resulted in significant loss of ACC2 potency (9c vs 9i-j). The terminal carbonyl group is also important for ACC activity. Propargylamine analogue 91 exhibited much weaker ACC potency than the corresponding acyl derivatives 9a and 9b. Methylurea 9m and methyl carbamate 9n analogues are potent and selective ACC2 inhibitors. Finally, while (S)-enantiomer **9p** is a potent and selective ACC2 inhibitor, the corresponding (R)-enantiomer (90) is 40-fold weaker in ACC2 activity. Differences in ACC activity were also observed between the dual ACC inhibitor 1 and its enantiomer.11

It is interesting that ACC2 selectivity is affected by changes in various positions of the molecule. For example, while **9b** is only modestly selective, ACC2 selectivity can be dramatically enhanced by replacing either the acetamide with urea (**9a**) or the phenyl with an isopropyl group (**9c**). Conversely, replacement of the thiazole moiety of **9c** with a phenyl group resulted in the loss of ACC2 selectivity (**12**). A similar loss of ACC2 selectivity was observed when the phenyl of **9c** was replaced with a pyridyl group (**9g**).

In general, this class of compounds exhibits good oral pharmacokinetic properties in rodents, characterized by high volume of distribution, low clearance, long half-life, and high bioavailability. Table 2 shows the pharmacokinetic profile of **9n**.

Since ACC catalyzes the synthesis of mCoA, mCoA levels are expected to be lower when animals are treated with a smallmolecule ACC inhibitor. In addition, since ACC2 is the predominant isoform in muscle, an ACC2-selective inhibitor should have more profound mCoA-lowering effects in muscle than liver tissues as reported in the ACC2 knockout mice.<sup>15</sup> The enantiomeric pair of inhibitors 90 and 9p was selected for acute in vivo mCoA study in Sprague-Dawley rats. As shown in Figure 2, active enantiomer 9p dose-dependently lowered mCoA in muscle (36% and 54% reduction at 10 and 50 mg/kg, respectively). A less robust but statistically significant reduction in mCoA levels in liver (26%) was also observed at 50 mg/kg dose, whereas there was no statistically significant effect on liver mCoA levels at 10 mg/kg. Not surprisingly, inactive enantiomer 90 had no effects on mCoA levels in muscle or in liver. A similar mCoA lowering effect was observed in muscle tissues of diet-induced obese mice when treated with active enantiomer **9p** (data not shown).

In conclusion, a class of structurally novel ACC inhibitors was discovered from HTS. A preliminary SAR study led to the identification of several potent and selective ACC2 inhibitors. A representative ACC2-selective inhibitor from this class demonstrated dose-dependent mCoA lowering in muscle tissues of rodent models. The correlation of in vitro potency with acute mCoA lowering between active and inactive enantiomers (**9p** and **9o**) indicates mechanism-based effects. Since mCoA plays a critical role in modulating lipid metabolism, ACC inhibition is expected to increase fatty acid oxidation and overall energy expenditure and ultimately increase insulin sensitivity in type



**Figure 2.** Effects on mCoA levels in muscle and liver of Sprague-Dawley rats (n = 6) after treatment with active enantiomer **9p** and inactive enantiomer **9o**. A mixture of 70% PEG-400/QS water was used as vehicle. Animals were free-fed overnight, and food was removed 1 h before dosing orally with **9o** and **9p** at 10 and 50 mg/kg. Two hours later, they were given a glucerna/cornstarch meal challenge. After an additional hour, the animals were sacrificed and tissues were harvested for mCoA measurement. The plasma drug levels were comparable for **9o** (1.33 and 5.33 µg/mL at 10 and 50 mg/kg, respectively) and **9p** (1.54 and 4.90 µg/mL at 10 and 50 mg/kg, respectively) treated animals.

2 diabetic/obese patients. Because  $ACC1^{-/-}$  mice are embryonically lethal, it is foreseeable that selective ACC2 inhibitors may provide superior safety profiles relative to nonselective ACC inhibitors.

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**Supporting Information Available:** Experimental procedures for the synthesis of the compounds in Table 1, characterization data for all final compounds and key intermediates, detailed protocol of human ACC1 and ACC2 assays, and LC/MS results for malonyl-CoA. This material is available free of charge via the Internet at http://pubs.acs.org.

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