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Structure–activity relationships for a novel series of thiazolyl phenyl ether derivatives exhibiting potent and selective acetyl-CoA carboxylase 2 inhibitory activity

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Abstract—Structure–activity relationships for a recently discovered thiazolyl phenyl ether series of acetyl-CoA carboxylase (ACC) inhibitors were investigated. Preliminary efforts to optimize the series through modification of the distal aryl ether moiety of the lead scaffold resulted in the identification of compounds exhibiting low-nanomolar potency and isozyme-selective ACC2 activity.

The obesity epidemic in developed countries is linked to an alarming rise in the prevalence of type 2 diabetes. Although the precise mechanisms underlying this association are unclear, the accumulation of fat in non-lipogenic tissues is increasingly recognized as a key causal factor in the development of insulin resistance, an antecedent of type 2 diabetes and other obesity-related disorders.[1–5] As critical regulators of fatty acid metabolism, acetyl-CoA carboxylases (ACCs) present attractive targets for the reduction of whole body lipid content and normalization of insulin sensitivity.[6–9] In humans and other mammals ACC exists in two tissue-specific isoforms. ACC1 catalyzes fatty acid synthesis in liver and adipose tissue while ACC2 regulates fatty acid oxidation in oxidative tissues such as heart and skeletal muscle.[10,11] Recent findings reported by Pfizer researchers for isozyme-nonselective ACC inhibitor **1** (CP-640186, Fig. 1)[12,13] as well as studies conducted by Wakil and co-workers on ACC2-deficient mice[14–16] have validated the therapeutic potential of ACC inhibition. Significantly, the latter studies demonstrated that while ACC2$^{-/-}$ mice were healthy and displayed a favorable metabolic profile, ACC1 knockout resulted in embryonic lethality,[17] suggesting that selective ACC2 inhibition may provide a safer therapeutic approach for chronic treatment of obesity, diabetes, and other symptoms of the metabolic syndrome.

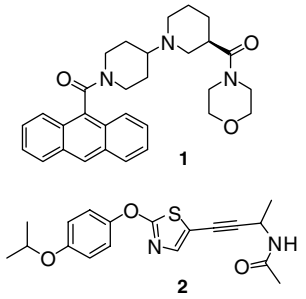

Figure 1.

Although several classes of isozyme-nonselective inhibitors, exemplified by **1**, have been described,[6,7] reports of isozyme-selective ACC2 inhibitors are lacking. Recently our laboratories reported the identification of compound **2** as a potent and selective inhibitor of ACC2.[18] Based on the promise of these preliminary findings we investigated the potential for further ACC2 potency improvements within the series through modification of the synthetically attractive isopropyl ether region of the lead scaffold.

Keywords: Acetyl-CoA carboxylase; Insulin resistance; Obesity; Type 2 diabetes.
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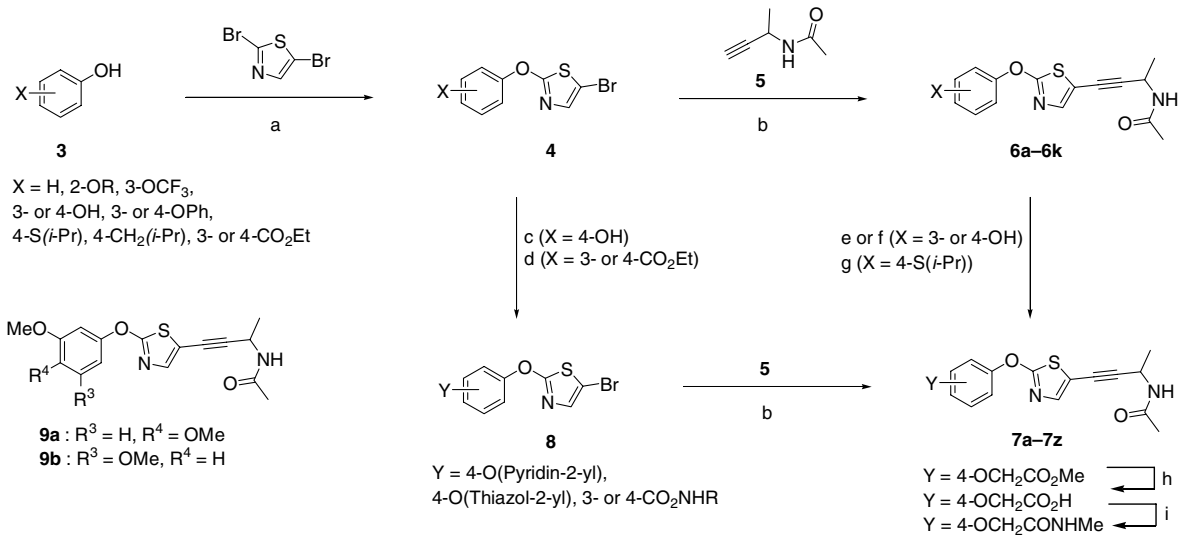
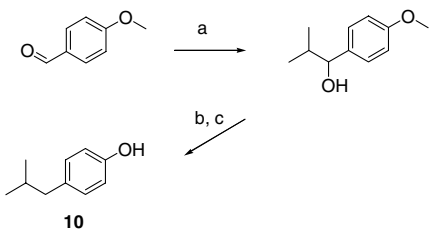


Scheme 1. Reagents and conditions: (a) K_2CO_3, DMF, 125–180 °C, conventional or microwave heating, 51–84%; (b) $Pd(PPh_3)_2Cl_2$ (cat.), CuI (cat.), Et_3N, THF, 80 °C in sealed pressure tube, 53–89%; (c) 2-fluoropyridine or 2-bromothiazole, K_2CO_3, DMF, 170 °C, microwave heating, 28–43%; (d) i—LiOH, EtOH, rt, 79–87%; ii—oxalyl chloride, DMF (cat.), CH_2Cl_2, rt; iii—RNH_2, Et_3N, CH_2Cl_2, rt, 85–96%, 2 steps; (e) ROH, diethyl azodicarboxylate, PPh_3, THF, rt, 24–67%; (f) *i*-PrNCO, Et_3N, THF, rt, 33%; (g) *m*-CPBA, $CHCl_3$, 0 °C, 2 h, 69%; (h) LiOH, MeOH, rt, 98%; (i) methylamine hydrochloride, TBTU, Hunig's Base, DMF, rt, 85%.

As depicted in Scheme 1, a convergent and general route for the rapid synthesis of target analogs was developed.[19] Selective displacement of 2,5-dibromothiazole by readily available phenols (**3**) at elevated temperatures provided intermediates **4** which were elaborated in good yields to the corresponding alkynyl products **6** and **7** under Sonogashira coupling conditions either directly or after subsequent functionalization as outlined. Requisite alkyne **5** was prepared from 3-hydroxy-3-methyl-1-butyne by the Ritter reaction using a published procedure.[20] With the exception of compound **6f**, all 4- and 3-substituted alkyl ethers represented in Table 1 (**7a**–**7k**, **7n**–**7p**, and **7v**–**7z**) were synthesized from advanced intermediates **6** (X = 3- or 4-OH), using the Mitsunobu reaction and an appropriate alcohol. Carbamate **7r** was also prepared from **6** (X = 4-OH) employing isopropyl isocyanate in the presence of triethylamine. Conversely, the synthesis of 2-alkoxy derivatives **6g**–**6i**, phenyl ethers **6d** and **6e**, and trifluoromethoxy analog **6f** utilized fully functionalized phenol precursors. Acid **7l** and amide **7m** were derived from ester **7k** by sequential saponification and coupling to methylamine in the presence of TBTU. Heteroaryl ethers **7i** and **7j** were accessed through the displacement of 2-fluoropyridine and 2-bromothiazole, respectively, with intermediate **4** (X = 4-OH) prior to palladium-catalyzed coupling with alkyne **5**. Similarly, ethyl esters **4** (X = 3- or 4-CO_2Et) were transformed to corresponding isopropyl and isobutyl amides before conversion to final products **7s**–**7u**. Synthesis of **6a**, the carbon-linked homolog of parent isopropyl ether **2**, required the preparation of 4-isobutylphenol **10**, which was synthesized according to the reaction sequence shown in Scheme 2. Treatment of 4-formylanisole with isopropylmagnesium bromide at 0 °C followed by reduction of the resulting alcohol with triethylsilane–trifluoroacetic acid provided 4-isobutylanisole which upon deprotection in the presence of boron tribromide gave the desired phenol (**10**) in good overall yield. Sulfur- and nitrogen-linked derivatives **6b** and **6c** were prepared as previously described.[18] In turn, oxidation of thioether **6b** under standard conditions with 3-chloroperbenzoic acid yielded sulfone **7q**.



Scheme 2. Reagents and conditions: (a) *i*-PrMgBr, THF, 0 °C, 57%; (b) Et_3SiH, CF_3COOH, CH_2Cl_2, rt, 97%; (c) BBr_3, CH_2Cl_2, 0 °C to rt, 94%.

Our initial structure–activity relationship (SAR) efforts sought to define preferred steric and physicochemical parameters for substitution at the C-4 isopropyl ether position in parent compound **2**. As shown in Table 1, the size and nature of distal ether adducts were key determinants of both potency and selectivity within the series. In general, a hydrophobic binding element was required to achieve optimal activity against ACC2. Incorporation of polar functionality into position 4 ether extensions led to uniform reductions in potency. Although acid, ester, amide, and amine side chains were particularly detrimental (**7k**–**7n**), the introduction of less hydrophilic ether and heteroaromatic groups was better tolerated (**7o**, **7p** vs **7e**, **7g**, and **7i** vs **6d**). As exemplified by compounds **6d** and **7a**–**7h** a variety of lipophilic ether groups exhibited excellent ACC2 activity. Compared to

Table 1. ACC inhibitory activity[a] for derivatives **6**, **7**, and **9**

Compound	X or Y	ACC1 IC_{50} (μM)	ACC2 IC_{50} (μM)	ACC1/ACC2[b]
1[c]	CP-640186	0.41	0.038	11
2	4-O(*i*-Pr)	>30	0.019	>1579
6a	4-CH_2(*i*-Pr)	1.12	0.081	14
6b	4-S(*i*-Pr)	0.37	0.055	7
6c	4-NH(*i*-Pr)	>30	0.150	>200
6d	4-OPh	0.26	0.011	24
6e	3-OPh	0.65	0.076	9
6f	3-OCF_3	>30	0.13	>227
6g	2-OMe	>30	1.32	>23
6h	2-OEt	>30	1.31	>23
6i	2-O(*i*-Pr)	>30	6.16	>5
6j	4-H	>30	1.96	>15
6k	4-OH	>30	1.70	>18
7a	4-OMe	>30	0.47	>64
7b	4-OEt	>30	0.037	>811
7c	4-OPr	0.14	0.004	35
7d	4-O(*i*-Bu)	0.23	0.010	23
7e	4-O(Cyclopentyl)	0.47	0.013	36
7f	4-O(Cyclohexyl)	0.12	0.016	7
7g	4-OCH_2(Cyclopentyl)	0.028	0.005	6
7h	4-OCH_2(Cyclohexyl)	0.086	0.027	3
7i	4-O(Pyridin-2-yl)	2.12	0.057	37
7j	4-O(Thiazol-2-yl)	6.79	0.29	23
7k	4-OCH_2CO_2Me	>30	1.62	>19
7l	4-OCH_2CO_2H	>30	>30	1
7m	4-$OCH_2CONHMe$	>30	26.50	>1
7n	4-O$(CH_2)_3NMe_2$	>30	>30	1
7o	4-O(THF[d]-3-yl)	>30	0.37	>82
7p	4-OCH_2(THF[d]-3-yl)	0.76	0.067	11
7q	4-SO_2(*i*-Pr)	3.70	4.05	1
7r	4-OCONH(*i*-Pr)	2.42	0.34	7
7s	4-CONH(*i*-Pr)	>30	19.48	>1
7t	4-CONH(*i*-Bu)	1.28	0.35	4
7u	3-CONH(*i*-Bu)	3.78	0.38	10
7v	3-OMe	>30	0.85	>35
7w	3-O(*i*-Pr)	0.066	0.014	5
7x	3-O(Cyclohexyl)	0.056	0.026	2
7y	3-O(*i*-Bu)	0.072	0.013	6
7z	3-O(THF[d]-3-yl)	1.15	0.21	6
9a	3,4-dimethoxy	>30	>30	1
9b	3,5-dimethoxy	>30	>30	1

[a] Inhibitory activity was determined using recombinant human ACC1 and ACC2 in an assay measuring ACC-mediated [^{14}C]CO_2 incorporation into malonyl-CoA. Detailed protocols are described in Ref. 18.

[b] ACC2 selectivity expressed as rounded ratio of ACC1 IC_{50}/ACC2 IC_{50}.

[c] Published IC_{50} values for compound **1** (Ref. 13) utilizing rat ACC1 (IC_{50} = 53 nM) and ACC2 (IC_{50} = 61 nM) enzyme sources were less ACC2 selective than corresponding values generated under our assay conditions.

[d] Tetrahydrofuran (THF).

2, position 4 side chains smaller than ethoxy were significantly less potent (**6j**, **6k**, and **7a**) while larger, chain-extended ether groups with enhanced flexibility resulted in 4- to 5-fold improvements in ACC2 activity (**7c** and **7g**). In fact, compounds **7c** (IC_{50} = 4 nM) and **7g** (IC_{50} = 5 nM) were among the most potent ACC2 inhibitors identified in our study. However, since productive binding to the ACC1 isozyme is also dependent on relatively large C-4 alkoxy substituents (**7c**–**7h** vs **7a**, **7b**, **2**), the excellent potency associated with these analogs was realized at the expense of ACC2 selectivity. Therefore, relative to other potent derivatives, only the ethyl and isopropyl ether adducts (**7b** and **2**) appear to provide degrees of hydrophobicity and steric compactness sufficient for both good potency (19–34 nM) and robust ACC2 selectivity (>800-fold).

Having defined general SAR patterns for C-4 aryloxy substitution we then investigated alternative linking groups (**6a**–**6c** and **7q**–**7t**). While replacement of the oxygen linker in **2** with carbon (**6a**), sulfur (**6b**), or nitrogen (**6c**) atoms produced good ACC2 activity as anticipated, only the nitrogen-linked variant exhibited ACC2 selectivity approximating that of the parent compound. In line with SAR findings discussed above, the slightly larger atomic size of sulfur relative to oxygen may explain the improved ACC1 activity and corresponding loss of selectivity observed for thioether **6b**. However, the relatively good ACC1 potency displayed by carbon-linked analog **6a** is more difficult to rationalize within this subseries. The introduction of sulfone (**7q**), carbamate (**7r**), and amide (**7s**) groups in place of oxygen resulted in more dramatic potency losses, although these effects

appear to be mitigated by incorporation of more flexible, hydrophobic side chains that compensate for the relative rigidity and polarity of these linkers (**7s** vs **7t**).

Regioisomeric preferences were also studied. In terms of overall activity, positions 3 and 4 on the phenyl ring were found to be preferred points of attachment for distal binding substituents. C-2 alkoxy ethers were uniformly less favored (**6g**–**6i**), particularly when larger, sterically demanding groups were introduced (**6i** vs **2** and **7w**). Generally, C-3 adducts displayed similar ACC2 potency, enhanced ACC1 activity, and consequently, reduced ACC2 selectivity in comparison to corresponding C-4 derivatives (**2** vs **7w**, **7d** vs **7y**, **7f** vs **7x**, and **7o** vs **7z**). Despite the inherent lack of selectivity for position 3 analogs, it is interesting that replacement of the C-3 methoxy group in **7v** with the similarly compact yet more hydrophobic trifluoromethoxy variant (**6f**) resulted in reasonably potent and selective ACC2 inhibition. These findings are consistent with trends observed for C-4 substitution and reveal a general requirement for sterically compact hydrophobic substituents, regardless of regiochemistry.

Finally, given the favorable ACC2 activity exhibited by monoalkoxy groups tethered to either the C-3 or C-4 position of the phenyl ring, we also preliminarily investigated whether further potency improvements might be gained by installing additional alkyl ether groups at these positions. Compared to methoxy derivatives **7a** and **7v**, 3,4- and 3,5-dimethoxy ethers **9a** and **9b**[21] displayed greatly reduced activity indicating that multiple distal alkoxy ring substituents have detrimental rather than additive effects.

In summary, we have investigated the tolerance for variation of the isopropyl ether moiety in recently discovered lead compound **2**. SAR requirements for potent, selective ACC2 inhibition were established. By tuning the size, nature, and regiochemistry of distal binding elements, exceptional levels of potency and selectivity were realized within the structural series. Sterically compact alkoxy substituents tethered to the C-4 position of the phenyl ring provided the most selective ACC2 activity (>800-fold) while larger, more flexible hydrophobic ethers produced superior, though non-selective ACC2 potency (IC_{50}s $\sim$ 4–5 nM). Although no modification in our study resulted in a better overall profile than parent compound **2**, the insights gained from this work will facilitate future optimization efforts in other domains of the lead template.

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19. Final compounds were isolated using either flash chromatography on silica gel or reverse-phase HPLC on a Waters Sunfire C18 column with a gradient of 5–95% acetonitrile: 0.1% aqueous trifluoroacetic acid. All analogs were in full agreement with proposed structures by ^{1}H NMR, HPLC, and MS (>95% purity).
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21. Compounds **9a** and **9b** were synthesized from commercially available 3,4- and 3,5-dimethoxy phenols according to reaction sequences described in Scheme 1.