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Phenoxy thiazole derivatives as potent and selective acetyl-CoA carboxylase 2 inhibitors: Modulation of isozyme selectivity by incorporation of phenyl ring substituents

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Abstract—A phenyl ring substitution strategy was employed to optimize the ACC2 potency and selectivity profiles of a recently discovered phenoxy thiazolyl series of acetyl-CoA carboxylase inhibitors. Ring substituents were shown to dramatically affect isozyme selectivity. Modifications that generally impart high levels of ACC2 selectivity (>3000-fold) while maintaining excellent ACC2 potency (IC_{50}s ~ 9–20 nM) were identified.

As critical regulators of fatty acid metabolism, acetyl-CoA carboxylases (ACCs) have attracted considerable attention from the pharmaceutical research community as targets for the treatment of metabolic syndrome.[1] Metabolic syndrome is characterized by a cluster of obesity-related disorders that collectively increase the risk of coronary heart disease and type-2 diabetes. Although the precise mechanisms are unclear, the accumulation of fat in non-lipogenic tissues is recognized as a primary causal factor in the development of insulin resistance, a key component of metabolic syndrome.[2] ACC catalyzes the carboxylation of acetyl-CoA to produce malonyl-CoA, a metabolic control signal acting as both substrate for de novo lipogenesis and an allosteric inhibitor of carnitine palmitoyltransferase1 (CPT-1) thereby blocking fatty acid entry into the mitochondria for β-oxidation. Consequently, the inhibition of ACC is expected to lower malonyl-CoA levels resulting in reduced fatty acid synthesis and increased fatty acid oxidation, leading to weight loss and improved insulin sensitivity. While several reports have validated the therapeutic potential of inhibiting ACC,[3] it remains unclear whether selective or nonselective inhibition of the enzyme's two isoforms will be most advantageous. Recently, genetic disruption studies in mice revealed that ACC2-deficient animals were healthy and displayed a favorable metabolic profile, while ACC1 knockout resulted in embryonic death.[4] A small molecule inhibitor that selectively inhibits ACC2 may therefore provide a safer therapeutic approach for chronic treatment of obesity, diabetes, and other symptoms of metabolic syndrome.

A primary goal of our research program has been the optimization of ACC2 potency and selectivity profiles for a recently discovered series of phenoxy thiazole inhibitors exemplified by lead compound **1**.[5,6] Investigations of the isopropyl ether region of **1** demonstrated that while sterically compact alkoxy substituents attached to the C-4 position of the phenyl ring were required for good ACC2 selectivity, a variety of larger, more flexible hydrophobic ether groups produced excellent, though nonselective, ACC2 potency (IC_{50}s ~ 4–10 nM).[6] These findings encouraged us to further probe structure–activity relationships (SAR) in the aryloxy region of the lead template in an effort to identify modifications that impart selectivity against the ACC1 isoform yet preserve or enhance established, potent ACC2 activity. In line with these objectives, the present report examines the effect of introducing C-2 phenyl ring substituents into our lead series of analogues (Fig. 1). In

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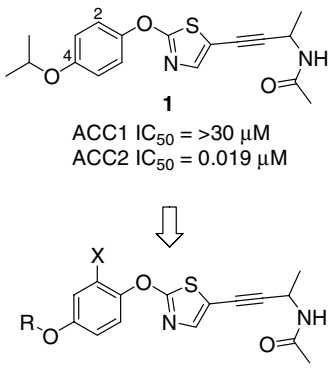
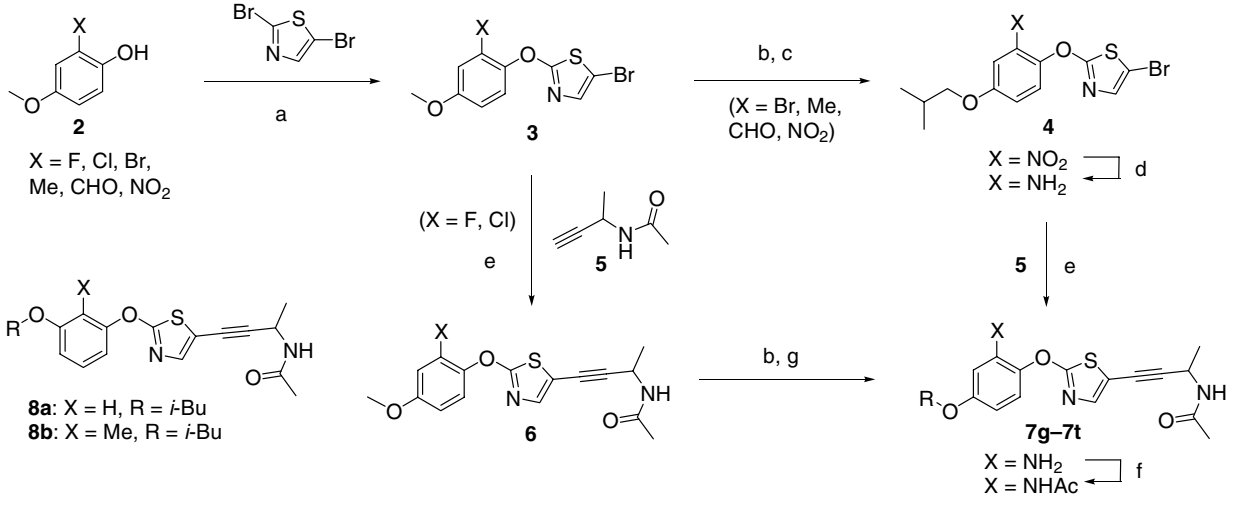


Figure 1. Lead ACC inhibitor **1** and ring substitution strategy.

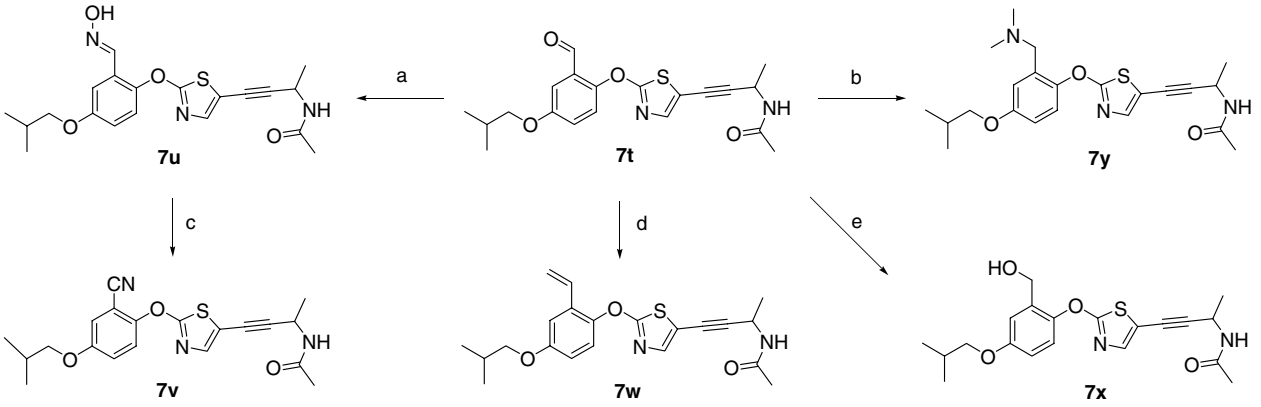
the absence of structural information, this approach was attractive since it enabled the investigation of unexplored substituent vectors and physicochemical parameters as potential avenues for improved profiles. An additional advantage of this course of SAR was the likelihood that C-2 ring substituents would alter the conformation of the phenyl moiety to varying degrees relative to neighboring domains in the parent scaffold allowing us to assess the consequences of such variations.[7]

C-2 functionalized derivatives **7g**–**7y** were synthesized according to methodologies described in Schemes 1–3.[8] These protocols represent adaptations of chemistry previously employed to prepare corresponding unsubstituted compounds **1** and **7a**–**7f**.[6] As shown in Scheme 1, selective displacement of 2,5-dibromothiazole with readily available phenols **2** provided intermediates **3**, which were elaborated to final products **7** utilizing two related reaction routes. All 2-chloro compounds **7g**–**7m** as well as 2-fluoro analogue **7n** were prepared from **3** by initial Sonogashira coupling to propargylic acetamide **5**[9] followed by deprotection and alkylation of the resulting phenols under Mitsunobu conditions. Alternatively, for bromo, methyl, nitro, and aldehyde 2-substituted analogues **7o**, **7p**, **7q**, and **7t**, respectively, initial deprotection of methyl ethers **3** with boron tribromide as well as subsequent alkylation sequences were carried out prior to attachment of alkynyl moiety **5**. Reduction of nitro intermediate **4** (X = NO_2) with potassium borohydride and CuCl followed by palladium-catalyzed coupling to **5** produced 2-amino derivative **7r**, which was then acylated to give 2-acetamide product **7s**. Similarly, straightforward modifications of aldehyde **7t** enabled the introduction of a variety of additional position 2 substituents (Scheme 2). Condensation of **7t** with hydroxylamine hydrochloride followed by activation and dehydration of the resulting oxime (**7u**) using methanesulfonyl chloride–pyridine provided nitrile analogue **7v**. In turn, reductive transformations of **7t** provided hydroxymethyl (**7x**) and dimethyl amino (**7y**) targets, while Peterson olefination yielded vinyl product **7w** as outlined. Phenol precursors required in the synthesis of compounds **7o** and **7p** were obtained in a convergent manner from 4-methoxyphenol as depicted in Scheme 3. Accordingly, bromination of 4-methoxyphenol produced 2-bromophenol **2o**, which was converted over a three-step reaction sequence to 2-methylphenol **2p**. Thus, lithiation of the methoxymethyl ether of **2o** with *n*-butyllithium at −78 °C followed by a methyl iodide quench and subsequent acidic hydrolysis of the MOM protecting group afforded 2-methylphenol **2p** in good overall yield. All other phenols **2** represented in Scheme 1 were obtained from commercial sources. 3-alkoxy compounds **8a** and **8b** were derived from resorcinol and 2-methylresorcinol, respectively, according to reaction sequences previously described.[6]

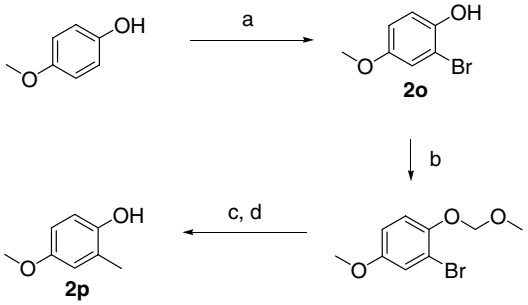
As a starting point in our phenyl ring substitution study, 2-position chloro groups were incorporated into both lead structure **1** as well as other series analogues containing a variety of C-4 alkoxy adducts previously determined to be potent but nonselective ACC inhibitors.[6] As



Scheme 1. Reagents and conditions: (a) K_2CO_3, DMF, 120–140 °C, 56–90%; (b) BBr_3, CH_2Cl_2, −78 °C to rt, 42–85%; (c) Method A (X = Br, Me): *i*-BuOH, DEAD, PPh_3, THF, rt, 79–91%; Method B (X = CHO, NO_2): *i*-BuBr, KI, K_2CO_3, DMF, 80 °C, 82–93%; (d) KBH_4, CuCl, MeOH, 0 °C to rt, 39%; (e) $Pd(PPh_3)_2Cl_2$ (cat.), CuI (cat.), Et_3N, THF, 75 °C, 19–83%; (f) acetyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 63%; (g) ROH, DEAD, PPh_3, THF, rt, 44–63%.



Scheme 2. Reagents and conditions: (a) hydroxylamine hydrochloride, EtOH, H_2O, 50 °C, 52%; (b) dimethylamine hydrochloride, $NaBH(OAc)_3$, NaOAc, HOAc, MeOH, rt, 37%; (c) methanesulfonyl chloride, pyridine, rt, 60%; (d) Me_3SiCH_2MgCl, Et_2O, 0 °C to rt, 2 h then 30% aq H_2SO_4, 21%; (e) $NaBH_4$, MeOH, −78 to 0 °C, 62%.



Scheme 3. Reagents and conditions: (a) bromine, $CHCl_3$, 0 °C to rt, 74%; (b) NaH, DMF, rt, 30 min then chloromethyl methyl ether, 0 °C to rt , 71%; (c) *n*-butyllithium (2.5 M in hexanes), Et_2O, −78 to 0 °C, 30 min then methyl iodide, −78 °C to rt, 94%; (d) 12 N HCl, MeOH, rt, 89%.

shown in Table 1, a comparison of activities between **1** and it's 2-chloro counterpart **7g** revealed that, other than a modest reduction in ACC2 potency, the 2-chloro modification was well tolerated and did not appear to significantly alter the favorable overall profile of the parent structure. However, while both of these analogues had ACC1 IC_{50} values exceeding 30 μM, closer inspection of the ACC1 dose–response curves showed that compound **1** and the 2-chloro variant **7g** exhibited 35% and 7% inhibition, respectively, at 30 μM, suggesting a selectivity-enhancing effect of 2-chloro substitution. Consistent with these observations, application of the 2-chloro modification to potent nonselective derivatives **7a**–**7f** was accompanied by dramatic reductions in ACC1 activity while the ACC2 potency was uniformly preserved, within 1- to 3-fold, in all contexts investigated (**7g**–**7m**).

Following the promise of these initial results we performed a more systematic evaluation of C-2 substitution in the context of 4-isobutoxy inhibitors **7a** and **7h**. 2-Fluoro entry **7n** displayed nonselective, potent activity resembling that of the unsubstituted parent analogue (**7a**), while 2-bromo derivative **7o** exhibited highly selective ACC2 activity approximating that of 2-chloro compound **7h**. We felt it unlikely that the difference in hydrophobic and electronic properties between these 2-halophenyl analogues was responsible for their divergent selectivities. Rather, the increased steric demands associated with 2-position chloro and bromo groups relative to a 2-fluoro substituent, were believed to be incompatible with the ACC1 isozyme. These conclusions are supported by the activity profile of 2-methyl analogue **7p**, which possesses steric and hydrophobic features comparable to 2-chloro variant **7h** but would be expected to impart differing electronic effects. The fact that the 2-chloro (**7h**) and 2-methyl (**7p**) compounds were similarly potent and selective ACC2 inhibitors, whereas the corresponding 2-fluoro and 2-unsubstituted derivatives (**7n** and **7a**, respectively) were nonselective, can therefore reasonably be ascribed to steric features. Likewise, the activity profiles for analogues incorporating relatively polar 2-position cyano (**7v**) and nitro (**7q**) groups, respectively, revealed that these substituents were also strongly disfavored by the ACC1 isoform yet were reasonably well tolerated by the ACC2 isozyme. Similarly, double bond-containing substituents exemplified by vinyl (**7w**), aldehyde (**7t**), and oxime (**7u**) C-2 derivatives were devoid of ACC1 activity, although these analogues also displayed reduced ACC2 potency. Methyl alcohol entry **7x** was also less active against ACC2. Interestingly, given the relative compactness of the 2-amino group in compound **7r**, the poor overall activity exhibited by this analogue indicates a lack of tolerance by the ACC2 isozyme for the basic character of the nitrogen adduct. More bulky acetamide (**7s**) and dimethylamino (**7y**) moieties in the C-2 position were also disfavored by both ACC isoforms.

Taken together, these data highlight contrasting tolerances for C-2 phenyl ring substitution between the ACC1 and ACC2 isozymes. Steric properties of position 2 adducts appear to be critical parameters for achieving ACC2 selectivity in the current series. Smaller, hydrophobic methyl and chloro groups were found to be optimal substituents for retaining excellent ACC2 potency and achieving high degrees of selectivity against ACC1. It is unclear whether the 2-substituent is directly involved in an unfavorable steric interaction with the ACC1 isozyme or if local conformational changes

Table 1. ACC inhibitory activity[a] for derivatives **1**, **7**, and **8**

Compound	R	X	ACC1 IC_{50}(μM)	ACC2 IC_{50}(μM)	ACC1/ACC2[b]
1	*i*-Pr	H	>30	0.019	>1500
7a	*i*-Bu	H	0.23	0.010	23
7b	Pr	H	0.140	0.004	35
7c	CH_2(cyclopropyl)	H	0.94	0.007	134
7d	Cyclohexyl	H	0.12	0.016	8
7e	CH_2(cyclohexyl)	H	0.086	0.027	3
7f	CH_2(THF-3-yl)[c]	H	0.76	0.067	11
7g	*i*-Pr	Cl	>30	0.069	>435
7h	*i*-Bu	Cl	>30	0.012	>2500
7i	Pr	Cl	>30	0.013	>2300
7j	CH_2(cyclopropyl)	Cl	>30	0.010	>3000
7k	Cyclohexyl	Cl	>30	0.034	>880
7l	CH_2(cyclohexyl)	Cl	>30	0.029	>1030
7m	CH_2(THF-3-yl)[c]	Cl	>30	0.14	>210
7n	*i*-Bu	F	0.34	0.011	31
7o	*i*-Bu	Br	>30	0.035	>855
7p	*i*-Bu	Me	>30	0.009	>3300
7q	*i*-Bu	NO_2	>30	0.070	>425
7r	*i*-Bu	NH_2	>30	15.80	>1
7s	*i*-Bu	NHCOMe	>30	>30	1
7t	*i*-Bu	CHO	>30	0.55	>55
7u	*i*-Bu	CH=NOH	>30	0.57	>50
7v	*i*-Bu	CN	>30	0.042	>710
7w	*i*-Bu	Vinyl	>30	0.26	>115
7x	*i*-Bu	CH_2OH	>30	1.00	>30
7y	*i*-Bu	CH_2NMe_2	>30	>30	1
8a	*i*-Bu	H	0.072	0.013	55.00
8b	*i*-Bu	Me	>30	0.018	>1665

[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. 5.
[b] ACC2 selectivity expressed as rounded ratio of ACC1 IC_{50}/ACC2 IC_{50}.
[c] Tetrahydrofuran (THF).

imposed on the phenoxy thiazolyl lead scaffold are responsible for the observed ACC2 selectivity-enhancing effects. In any case, the ACC1 isoform is more sensitive to C-2 substitution than is the ACC2 isozyme and the introduction of groups larger than hydrogen or fluorine was shown to abolish ACC1 activity.

Given the remarkable selectivity-modulating effects of C-2 ring substitution within the 4-alkoxy inhibitor series, the 2-methyl analogue (**8b**) of 3-isobutoxy inhibitor **8a** was also prepared. We previously demonstrated that a series of 3-alkoxy derivatives exemplified by **8a** characteristically exhibit potent, though nonselective, ACC inhibition.[6] As shown in Table 1, incorporation of a 2-methyl group (**8b**) in this context also resulted in a loss of ACC1 activity and retention of ACC2 potency. These findings suggest that C-2 substituents may provide general selectivity-enhancements in our lead series with the potential for improving ACC2 selectivity profiles regardless of structural context.

In conclusion, we have shown that the introduction of C-2 phenyl ring substituents is an effective strategy for modulating isozyme selectivity profiles in the current ACC inhibitor series. The ACC1 isoform was found to be generally intolerant to ring substitution, whereas a variety of relatively hydrophobic, sterically compact substituents were well tolerated by the ACC2 isoform. Consequently, 2-position chloro or methyl groups, for example, effectively serve as ACC2 selectivity 'switches' that impart high selectivity against ACC1 yet conserve ACC2 potency in otherwise nonselective contexts. The application of this strategy has resulted in enhanced overall profiles with respect to both ACC2 selectivity (>3000-fold) and ACC2 potency (single-digit nanomolar) in the current lead series. Furthermore, the selectivity-enhancing effects associated with these modifications were shown to be general across a range of structural analogues.

References and notes

1. (a) Harwood, H. J., Jr. *Expert Opin. Ther. Targets* **2005**, *9*, 267; (b) Tong, L. *Cell Mol. Life Sci.* **2005**, *62*, 1784; (c) Harwood, H. J., Jr. *Curr. Opin. Invest. Drugs* **2004**, *5*, 283; (d) Burn, P.; Shi, Y. *Nat. Rev. Drug Disc.* **2004**, *3*, 695.
2. (a) Unger, R. H. *Endocrinology* **2005**, *144*, 5159; (b) Lazar, M. A. *Science* **2005**, *307*, 373; (c) Hulver, M. W.; Berggren, J. R.; Cortright, R. N.; Dudek, R. W.; Thompson, R. P.; Pories, W. J.; MacDonald, K. G.; Cline, G. W.; Shulman, G. I.; Dohm, G. L.; Houmard, J. A. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *284*, E741; (d) Friedman, J. *Nature* **2002**, *415*, 268; (e) Arner, P. *Diabetes Metab. Res. Rev.* **2002**, *18*, S5.
3. (a) Oh, W.; Abu-Elheiga, L.; Kordari, P.; Gu, Z.; Shaikenov, T.; Chirala, S. S.; Wakil, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 1384; (b) Treadway, J. L.; McPherson, R. K.; Petras, S. F.; Shelly, L. D.; Frederick, K. S.; Sagawa, K.; Perry, D. A.; Harwood, H. J., Jr. 64th Annual Meeting

and Scientific Sessions of the American Diabetic Asssociation, Orlando, FL, June 4–8, 2004; (c) Harwood, H. J., Jr.; Petras, S. P.; Shelly, L. D.; Zaccaro, L. M.; Perry, D. A.; Makowski, M. R.; Hargrove, D. M.; Martin, K. A.; Tracey, W. R.; Chapman, J. G.; Magee, W. P.; Dalvie, D. K.; Soliman, V. F.; Martin, W. H.; Mularski, C. J.; Eisenbeis, S. A. *J. Biol. Chem.* **2003**, *278*, 37099; (d) Abu-Elheiga, L.; Oh, W.; Kordari, P.; Wakil, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 10207; (e) Abu-Elheiga, L.; Matzuk, M. M.; Abo-Hashema, K. A. H.; Wakil, S. J. *Science* **2001**, *291*, 2613.

4. Abu-Elheiga, L.; Matzuk, M. M.; Kordari, P.; Oh, W.; Shaikenov, T.; Gu, Z.; Wakil, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 12011.
5. Gu, Y. G.; Weitzberg, M.; Clark, R. F.; Xu, X.; Li, Q.; Zhang, T.; Hansen, T. M.; Liu, G.; Xin, Z.; Wang, X.; Wang, R.; McNally, T.; Camp, H.; Beutel, B. A.; Sham, H. L. *J. Med. Chem.* **2006**, *49*, 3770.
6. Clark, R. F.; Zhang, T.; Xin, Z.; Liu, G.; Wang, Y.; Hansen, T. M.; Wang, X.; Wang, R.; Zhang, X.; Frevert, E. U.; Camp, H. S.; Beutel, B. A.; Sham, H. L.; Gu, Y. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6078.
7. (a) Rovnyak, G.; Andersen, N.; Gougoutas, J.; Hedberg, A.; Kimbal, S. D.; Malley, M.; Moreland, S.; Porubcan, M.; Pudzianowski, A. *J. Med. Chem.* **1991**, *34*, 2521; (b) Green, A. L.; Marshall, I. G. *Nature* **1970**, *228*, 1211; (c) Clark, E. R.; Dawes, P. M.; Williams, S. G. *Br. J. Pharmacol. Chemother.* **1968**, *32*, 113.
8. 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 analogues were in full agreement with proposed structures by ^{1}H NMR, HPLC, and MS (>95% purity).
9. Gardner, J. N. *Can. J. Chem.* **1973**, *51*, 1416.