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Potent biphenyl- and 3-phenyl pyridine-based inhibitors of acetyl-CoA carboxylase

Tasir S. Haque [a,*], Ningning Liang [a], Rajasree Golla [b], Ramakrishna Seethala [b], Zhengping Ma [c], William R. Ewing [a], Christopher B. Cooper [a], Mary Ann Pelleymounter [c], Michael A. Poss [a], Dong Cheng [c]

[a] Department of Discovery Chemistry, Bristol-Myers Squibb Research and Development, PO Box 4000, Princeton, NJ 08543-4000, USA
[b] Department of Applied Biotechnologies, Bristol-Myers Squibb Research and Development, PO Box 4000, Princeton, NJ 08543-4000, USA
[c] Department of Discovery Biology, Bristol-Myers Squibb Research and Development, PO Box 4000, Princeton, NJ 08543-4000, USA

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ABSTRACT

We report the synthesis and enzymatic evaluation of potent inhibitors of acetyl-CoA carboxylases (ACCs) containing biphenyl or 3-phenyl pyridine cores. These compounds inhibit both ACC1 and ACC2, or are moderately selective for either enzyme, depending on side chain substitution. Typical activities of the most potent compounds in this class are in the low double-digit to single-digit nanomolar range in in vitro assays using human ACC1 and ACC2 enzymes.

Obesity is not only a major public health issue for the United States,[1] but also for the world in general.[2] In the United States the incidence of obesity in adults doubled (and in children and adolescents tripled) between 1980 and 2002. In 2004, 32.2% of adults over age 20 were classified as obese.[1] Obesity is associated with a number of serious diseases, including type 2 diabetes, coronary heart disease, dyslipidemia, and hypertension.

The Acetyl-CoA Carboxylase (ACC) enzymes are potential points of intervention for the treatment of obesity. Mammalian ACC1 and ACC2 are large (with molecular masses of 265 kDa and 280 kDa, respectively), functionally multicomponent enzymes that catalyze the ATP-dependent conversion of acetyl-CoA to malonyl-CoA.[3] The ACC enzymes are believed to play pivotal roles in energy homeostasis, not only through direct participation in fatty acid synthesis, but also through regulation of fatty acid β-oxidation. Malonyl-CoA is a key metabolite that serves as a precursor for de novo fatty acid synthesis in the liver and adipose tissue.[4] In heart, muscle, and liver tissues, where fatty acids are utilized as a fuel source, malonyl-CoA also serves as a sensor to gauge the rate of mitochondrial fatty acid β-oxidation through an allosteric inhibition of carnitine palmitoyl-CoA transferase (CPT-1).[5]

There has been debate regarding the desirability of a non-selective inhibitor of the ACC isoforms versus a selective inhibitor of the ACC2 isoform for the treatment of obesity. Intracellularly, ACC1 is localized in the cell cytosol and is believed to be responsible for generation of malonyl-CoA destined for fatty acid synthesis.[6] ACC2 is localized at the mitochondrial membrane,[7] and is believed to be responsible for generation of the malonyl-CoA that allosterically inhibits CPT-1.[6] Therefore, inhibition of ACC1 may result in decreased fatty acid synthesis, whereas inhibition of ACC2 may result in increased fatty acid oxidation. Inhibition of both ACC enzymes may combine the benefits of decreased synthesis and increased consumption of fatty acids, which may be required for robust efficacy in therapeutic weight loss.[8] On the other hand, the safety profile of such a dual-isoform inhibitor is unclear. While ACC2 knockout mice are healthy, viable, lean, and appear to exhibit resistance to obesity induced by a high-fat diet,[9] the ACC1 knockout in mice is embryonically lethal.[10] We chose to pursue both pan-ACC and isoform-selective inhibitors, with the ultimate goal of evaluating the inhibitors in the appropriate rodent obesity models in the future.

A number of mammalian ACC inhibitors have been reported in the patent and scientific literature,[11] examples of which are shown in Figure 1. Soraphen A[12] is a polyketide natural product that acts via inhibition of the eukaryotic BC domain of ACC, but lacks potency against bacterial BC subunits. Pfizer reported the synthesis and ACC inhibition of CP-640186, which displays inhibitory activity against both human ACC isoforms.[13] Abbott has reported a number of both pan-ACC and ACC2-selective inhibitors,[14,15] two

* Corresponding author. Tel.: +1 609 252 4273.
E-mail address: tasir.haque@bms.com (T.S. Haque).

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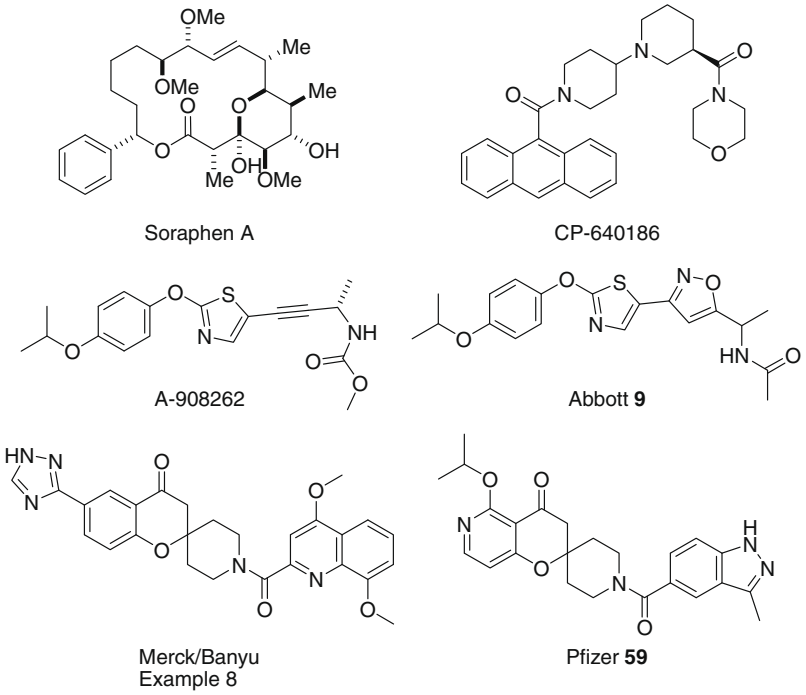
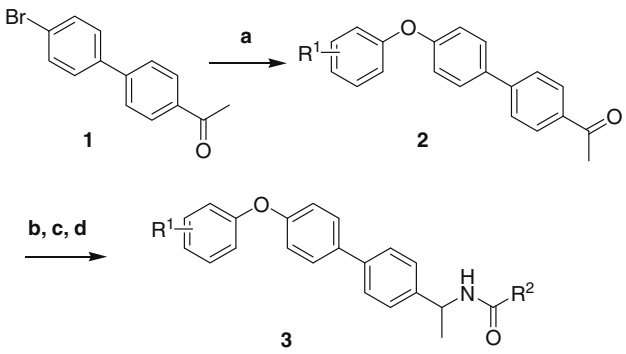


Figure 1. Structures of several reported ACC inhibitors.

of which are shown in Figure 1.[16] Several groups have also reported potent ACC inhibitors based on a spirochromanone core, including Example 8 reported by Merck and Banyu Pharmaceuticals,[17] related series (not shown) from Torrent Pharmaceuticals[18] and Takeda,[19] and the independently derived Pfizer compound **59**.[20] Herein we disclose the discovery of ACC inhibitors based on biphenyl and 3-phenyl pyridine chemotypes as shown in Figure 2. These chemotypes are synthetically readily accessed, and provide templates that can be easily modified for building structure–activity relationships regarding inhibitory potency and selectivity for the two ACC enzymes.

Our initial efforts focused on exploring the right and left sides of the biphenyl core at the same time using a positional scanning approach, holding one side constant while varying the other side. The right-hand side of the molecule (as shown in Fig. 3) was fixed as the acetamide, and the left-hand side was varied through coupling of 1-(4′-bromobiphenyl-4-yl)ethanone with a variety of substituted phenols under Ullmann coupling conditions (Scheme 1). Following elaboration to the desired target acetamides, the compounds were evaluated for inhibitory activity against both human ACC1 and ACC2 enzymes.[21] Data for these compounds (**3a**–**3n**) is shown in Table 1. Substitution at both the *meta* and *para* (3- and 4-aryl) R^1 positions resulted in potent ACC inhibitors. Phenoxy ethers at either position were potent pan-ACC inhibitors, as shown by **3d** and **3n**. Compounds containing the relatively small ethoxy group (**3a** and **3l**) or methoxy group (**3k**) at either position resulted in loss of potency, especially against ACC1. It is interesting to note that two compounds with alkyl substitution at the *para* position displayed good to excellent selectivity for ACC1 (**3g** and **3i**, 24-fold and >300-fold, respectively). Many of the alkoxy or aryloxy-substituted compounds were approximately equipotent for the two enzymes. However, compounds **3a**, **3k**, and **3l**; with small alkoxy groups at R^1 at either the 3- or 4-aryl positions, exhibited 14-fold, greater than 80-fold, or 84-fold selectivity, respectively for ACC2. These results suggest that careful selection of R^1 substituent can 'tune' compounds of this series towards ACC1-selective, ACC2-selective, or pan-ACC inhibition.



Scheme 1. Synthesis of biphenyl analogues. Reagents and conditions: (a) R^1-substituted phenol, Cs_2CO_3, CuI, *N*,*N*-dimethylglycine hydrochloride, 1,4-dioxane, 90 °C, 16 h; (b) NH_3, $Ti(OiPr)_4$, EtOH, 50 °C, 16 h; (c) $NaBH_4$, 2 h, rt; (d) R^2–COOH, DIC, HOBt, DIEA, CH_2Cl_2, rt, 16 h.

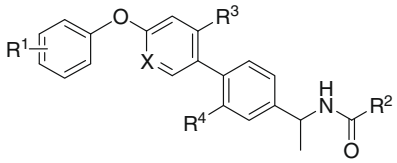


Figure 2. Core chemotype chosen for SAR exploration. X = CH, N.

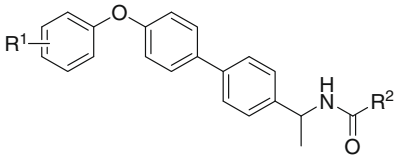


Figure 3. Biphenyl core used for the exploration of ACC inhibition via variation at R^1 and R^2.

Table 1
Human ACC1 and ACC2 inhibitory activity for biphenyl series

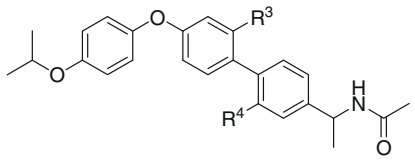
	R^1	R^2	Human ACC1 IC_{50}[a] (nM)	Human ACC2 IC_{50}[a] (nM)
3a	4-OCH_2CH_3	CH_3	1630	119
3b	4-$O(CH_2)_2CH_3$	CH_3	17	14
3c	4-$OCH(CH_3)_2$	CH_3	17	33
3d	4-OPh	CH_3	14	7
3e	4-OCH_2Ph	CH_3	>30,000	>30,000
3f	4-$(CH_2)_2CH_3$	CH_3	81	114
3g	4-CH_2Phe	CH_3	39	945
3h	4-COPh	CH_3	35	113
3i	4-$(CH_2)_2OCH_3$	CH_3	89	>30,000
3j	4-(5,6,7,8-Tetrahydronaphthalen-2-ol)	CH_3	140	268
3k	3-OCH_3	CH_3	>30,000	373
3l	3-OCH_2CH_3	CH_3	8580	102
3m	3-$O(CH_2)_3CH_3$	CH_3	13	12
3n	3-OPh	CH_3	41	16
3o	4-$O(CH_2)_2CH_3$	CH_2CH_3	47	202
3p	4-$O(CH_2)_2CH_3$	$(CH_2)_2CH_3$	2770	>30,000
3q	4-$O(CH_2)_2CH_3$	$(CH_2)_3CH_3$	>30,000	>30,000
3r	4-$O(CH_2)_2CH_3$	$CH(CH_3)_2$	188	214
3s	4-$O(CH_2)_2CH_3$	CH_2OCH_3	753	718
3t	4-$O(CH_2)_2CH_3$	$CH(OH)CH_3$ (racemic)	2060	1840
3u	4-$O(CH_2)_2CH_3$	Cyclopropyl	296	550
3v	3-$O(CH_2)_2CH_3$	Pyrazol-4-yl	36	609
3w	4-$O(CH_2)_2CH_3$	OCH_2CH_3	>30,000	3100

[a] Values are the averages of 2–4 experiments, with IC_{50} values typically reproducible within twofold.

We concurrently explored the right-hand side of the chemotype, while holding the left-hand side constant as the 4-propoxyphenyl substituent. The data for these compounds (**3o**–**3w**) is shown in Table 1. For the most part only small alkyl groups were tolerated, as shown in the trend from $R^2 = CH_3$ (**3b**, ACC1 IC_{50} = 17 nM, ACC2 IC_{50} = 14 nM) to $R^2 = (CH_2)_3CH_3$ (**3q**, inactive vs both ACC1 and ACC2). Cyclic groups were only moderately tolerated, with the pyrazol-4-yl amide (**3v**, with 3-$O(CH_2)_2CH_3$ at R^1) displaying 17-fold selectivity for ACC1. The ethyl carbamate **3w** was essentially inactive against both enzymes.

In addition to the left side and right side variations, we wanted to explore the possibility of substitution on the two biphenyl rings of the core. Such substitution would be expected to increase the degree of 'twist' between the planes of the two phenyl groups, and might also affect potency of the compounds via direct steric interaction with the enzyme binding site. Three compounds were made in this series, and are compared to the unsubstituted analogue in Table 2. Substitution at R^3 (**4a**) had no effect on potency for either enzyme, while substitution at R^4 (**4b**) resulted in a loss of potency, especially against ACC1. The difference in potency observed for substitution at R^3 versus R^4 suggests a direct steric interaction with the binding site for compound **4b**. One would have expected **4a** and **4b** to be equipotent if the only factor affecting potency were the change in the torsion angle between the two central aromatic rings. As shown by **4c**, substitution at both R^3 and R^4 restores some of the potency against both enzymes, especially for ACC2. Overall, these results suggest that substitution of the central aromatic groups in the biphenyl series could result in both potent and selective inhibitors.

Table 2
R^3- and R^4-substituted biphenyl compounds **4**



	R^3	R^4	Human ACC1 IC_{50}[a] (nM)	Human ACC2 IC_{50}[a] (nM)
3c	H	H	17	33
4a	CH_3	H	16	35
4b	H	CH_3	2490	303
4c	CH_3	CH_3	592	88

[a] Values are the averages of 2–4 experiments, with IC_{50} values typically reproducible within twofold.

A second series of compounds designated the '3-phenyl pyridine series' (Fig. 4), was developed both to explore the effect of including a heteroaromatic group in the core, and to modulate the solubility characteristics of the molecules. We specifically chose to explore the 3-phenyl pyridine series both to display the nitrogen in a region similar to that found in the nitrogen of the thiazoles of known inhibitors A-908262 and Abbott **9** (Fig. 1), and for the synthetic accessibility of the target molecules. Compounds in this series were synthesized as shown in Scheme 2.

The ethers of the 3-phenyl pyridine series generally displayed SAR trends similar to the comparable compounds from the biphenyl series, with the most potent ACC2 inhibitor corresponding to the 4-n-propoxyphenyl ether (**10b**, Table 3). In general the compounds in the 3-phenyl pyridine series were slightly less potent than their corresponding compounds from the biphenyl series. As shown with compound **10a**, substitution with a small 4-ethoxy group at R^1 produced a compound that displayed moderate potency towards ACC2 and good selectivity (at least 100-fold) over ACC1 (ACC1 IC_{50} >30,000 nM, ACC2 IC_{50} = 274 nM). Compounds substituted with the optimal group for ACC2 inhibition for the 3-phenyl pyridine series (**10b**, R^1 = 4-$O(CH_2)_2CH_3$) displayed ~5-fold selectivity for ACC2 (ACC1 IC_{50} = 110 nM, ACC2 IC_{50} = 18 nM). This is in contrast to compounds in the biphenyl series, where ana-

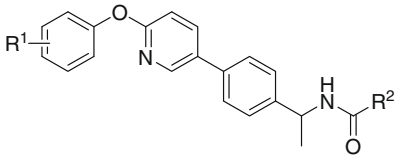
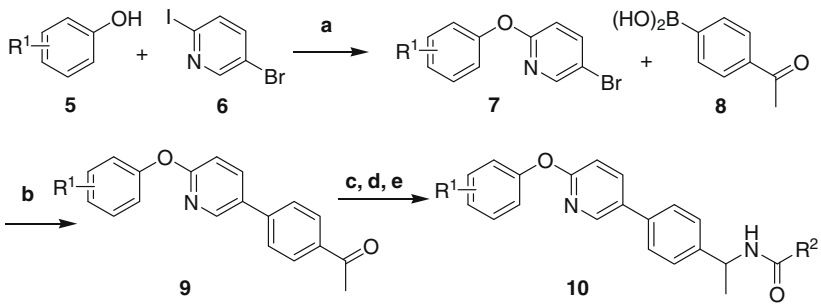


Figure 4. 3-Phenyl pyridine core used for the exploration of ACC inhibition via variation at R^1 and R^2.



Scheme 2. Synthesis of 3-phenyl pyridine analogues. Reagents and conditions: (a) Cs_2CO_3, CuI, *N,N*-dimethylglycine hydrochloride, 1,4-dioxane, 90 °C, 16 h; (b) $Pd[P(Ph)_3]_4$, K_3PO_4, DMF, 120 °C, 16 h; (c) NH_3, $Ti(OiPr)_4$, EtOH, 50 °C, 16 h; (d) $NaBH_4$, 2 h, rt; (e) R^2–COOH, DIC, HOBt, DIEA, CH_2Cl_2, rt, 16 h.

Table 3
Human ACC1 and ACC2 inhibitory activity for 3-phenyl pyridine series

	R^1	R^2	Human ACC1 IC_{50}[a] (nM)	Human ACC2 IC_{50}[a] (nM)
10a	4-OCH_2CH_3	CH_3	>30,000	274
10b	4-$O(CH_2)_2CH_3$	CH_3	110	18
10c	4-$OCH(CH_3)_2$	CH_3	415	93
10d	3-OPh	CH_3	49	32
10e	4-OCH_2Ph	CH_3	58	117
10f	4-$O(CH_2)_2CH_3$	CH_2CH_3	69	35
10g	4-$O(CH_2)_2CH_3$	$(CH_2)_2CH_3$	4200	494
10h	4-$O(CH_2)_2CH_3$	$CH(CH_3)_2$	451	156
10i	4-$O(CH_2)_2CH_3$	Cyclopropyl	319	141
10j	4-$O(CH_2)_2CH_3$	$(CH_2)_3CH_3$	>30,000	1510
10k	4-$O(CH_2)_2CH_3$	$CH_2O\ CH_3$	>30,000	881
10l	4-$O(CH_2)_2CH_3$	Pyrazol-4-yl	>30,000	2540
10m	4-$O(CH_2)_2CH_3$	OCH_2CH_3	8150	227

[a] Values are the averages of 2–4 experiments, with IC_{50} values typically reproducible within twofold.

logs having the optimal R^1 substitution such as **3b** were equipotent against both enzymes.

Exploration of the acyl, or 'right-side' SAR in the 3-phenyl pyridine series is shown in Table 3, entries **10f**–**10m**. Small amides appear to be optimal at R^2, with **10b** and **10f** (acetamide and *n*-propionamide, respectively) being amongst the most potent inhibitors of either enzyme, and both displaying weak selectivity for inhibition of ACC2 (sixfold and twofold, respectively). Unlike the biphenyl series, the pyrazol-4-yl amide **10l** was inactive against both ACC enzymes. The ethyl carbamate, essentially inactive against both enzymes in the biphenyl series (**3w**, IC_{50} >3000 nM for ACC1 and ACC2), displayed moderate potency against ACC2 and selectivity over ACC1 in the (pyridin-3-yl)phenyl series (**10m**, ACC1 IC_{50} = 8150 nM, ACC2 IC_{50} = 227 nM).

Finally, researchers at Abbott previously noted that one enantiomer of their series was considerably more potent than the other enantiomer.[14] We separated and tested the two enantiomers of **10b**. The results are shown in Table 4, and demonstrate that for the 3-phenyl pyridine series the (*S*)-enantiomer **11a** is at least ~100-fold more potent against both ACC enzymes than the (*R*)-enantiomer **11b**.[22]

In summary, we have identified two series of ACC inhibitors based on a biphenyl or 3-phenyl pyridine core. Compounds with modest to good selectivity for both ACC isoforms were identified, and SAR was explored at a number of points on both cores. Small alkoxy R^1 groups at both the 3- and 4-positions R^1 generally afforded potent ACC inhibitors with the trend of smaller alkoxy groups providing greater ACC2 selectivity. Phenoxy substitution was also well-tolerated at R^1, yielding pan-ACC inhibitors **3d**, **3n**, and **10d**. At R^2 there was a clear preference for methyl and ethyl amides over larger alkyl amides, implying a relatively small binding pocket at this position. However, the good ACC1 potency of **3v**, with R^2 = pyrazol-4-yl, suggests that small heterocycles may also be accommodated at this position and could provide isoform selectivity. Both the biphenyl and 3-phenyl pyridine cores afforded potent ACC inhibitors. As shown with compounds **4a**–**4c**, substitution at R^3 on the central aryl groups is tolerated, suggesting an additional site for modification to enhance potency, solubility, and PK and PD characteristics of the two series. The most active compounds **3b**, **3d**, **3m**, and **11a** displayed low nanomolar potency for the human ACC enzymes. The results described above suggest a variety of possibilities for further optimization of potency and/or selectivity of the two series.

Table 4
Comparison of enantiomers of **10b** for 3-phenyl pyridine core

	Enantiomer	Human ACC1 IC_{50}[a] (nM)	Human ACC2 IC_{50}[a] (nM)
11a	(*S*)	35	8
11b	(*R*)	>30,000	777

[a] Values are the averages of 2–4 experiments, with IC_{50} values typically reproducible within twofold.

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21. The ACC inhibitors in the current paper were evaluated by the ACC/Fatty-Acid-Synthase (FAS)-Coupled Assay according to Seethala et al. (*Anal. Biochem.* **2006**, *58*, 257) with minimal modifications. Briefly, the assay buffer (50 mM HEPES pH 7.5, 10 mM sodium citrate, 20 mM $MgCl_2$, 6 mM $NaHCO_3$) and substrate mixture (containing 2.4 μM [^{3}H] acetyl-CoA (PerkinElmer, NET-290) and 47.6 μM acetyl-CoA, 100 μM NADPH and 0.125 mM ATP in Assay Buffer) were all made fresh on the day of assay from stock solutions. Human ACC1 and human ACC2 were recombinant enzymes expressed in and purified from a bacculovirus system (*Protein Expr. Purif.* **2007**, *51*, 11). To each well containing 0.5 μL of compound in DMSO or DMSO as control in a 384-well phospholipid FlashPlate® (PerkinElmer) was added 30 μL of a solution of ACC (2–4.5 nM) and FAS (1 μg/assay) enzymes in assay buffer. After a 10 min incubation, the reaction was started via addition of 20 μl of substrate mixture. The reaction was carried out for 30 min at room temperature. After incubation, the reaction was quenched with the addition of 10 μl of 200 mM EDTA (~33 mM final concentration). The [^{3}H]-palmitic acid produced was determined by counting in a TopCount instrument (PerkinElmer). The IC_{50} for each compound was calculated using a logistic 4 parameter fit equation: $y = A + ((B - A)/(1+((C/x)\text{^}D)))$ in an in house developed data processing program TOOLSET.
22. The identity of single enantiomers was confirmed by synthesis of the (*S*)-enantiomer using chiral *tert*-butylsulfinimine reductive amination procedure (Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett*. **1999**, *40*, 6709), and comparison to enantiomers separated by chiral HPLC.