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The synthesis and structure–activity relationship studies of selective acetyl-CoA carboxylase inhibitors containing 4-(thiazol-5-yl) but-3-yn-2-amino motif: Polar region modifications

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Abstract—The structure–activity relationship study focused on the polar region of the HTS hit A-80040 (**1**) producing several series of potent and selective ACC2 inhibitors. The SAR suggests a compact lipophilic pocket that does not tolerate polar and ionic groups. Replacement of the hydroxyurea group with isoxazoles improves ACC2 selectivity while maintaining potency. Variations at the propargylic site of **11a** reduce ACC2 potency.

Metabolic syndrome and its associated insulin resistance have been linked to the emerging plague of type II diabetes and coronary heart disease. One potential therapeutic approach to address insulin resistance is to prevent the accumulation of fat in non-lipogenic tissues,[1] and inhibition of acetyl-CoA carboxylase (ACC) has been suggested as an attractive mechanism for this purpose.[2,3] ACC, which catalyzes the biotin-dependent carboxylation of acetyl-CoA to form malonyl-CoA (mCoA), has two isoforms with distinct cellular localizations and tissue distributions.[4,5] ACC1, a cytosolic enzyme highly expressed in liver and lipogenic tissues, is a rate-limiting enzyme for fatty acid synthesis, whereas ACC2, highly expressed in oxidative tissues such as muscle, is located in the outer membrane of mitochondria. It has been suggested that the mCoA produced by ACC2 regulates carnitine palmitoyl-transferase (CPT1),[6] which transfers long chain fatty acyl-CoAs into the mitochondria for oxidation.[7–9] Thus, inhibition of both ACC isoforms is expected to lower mCoA levels, reduce fatty acid synthesis, and increase fatty acid oxidation leading to improved insulin sensitivity. Genetic studies have shown that ACC1 knockout mice are lethal at the embryonic stage, whereas ACC2 knockout mice are healthy and maintain normal development and life expectancy. Furthermore, despite consuming more food, ACC2 knockout mice had lower body fat mass than their wild-type counterparts and were protected from high fat induced obesity and insulin resistance.[6,10–12] It is conceivable that selective ACC2 inhibition may provide a superior safety profile. As a result, our research efforts have been focused on identifying a selective ACC2 inhibitor as a potential therapeutic agent for type II diabetes and obesity. Recently, we reported the discovery of **1**[13] (A-80040, Fig. 1) and detailed structure–activity relationship studies on the lipophilic region.[14] In this communication, we describe the effect of modification of the polar region of **1** on ACC2 inhibitory activity and selectivity.

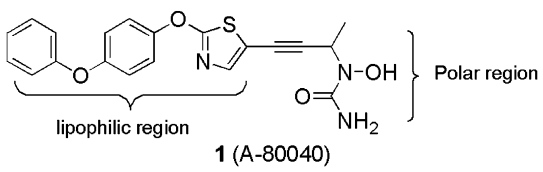

Figure 1. Structure of ACC HTS hit from Abbott compound collection.

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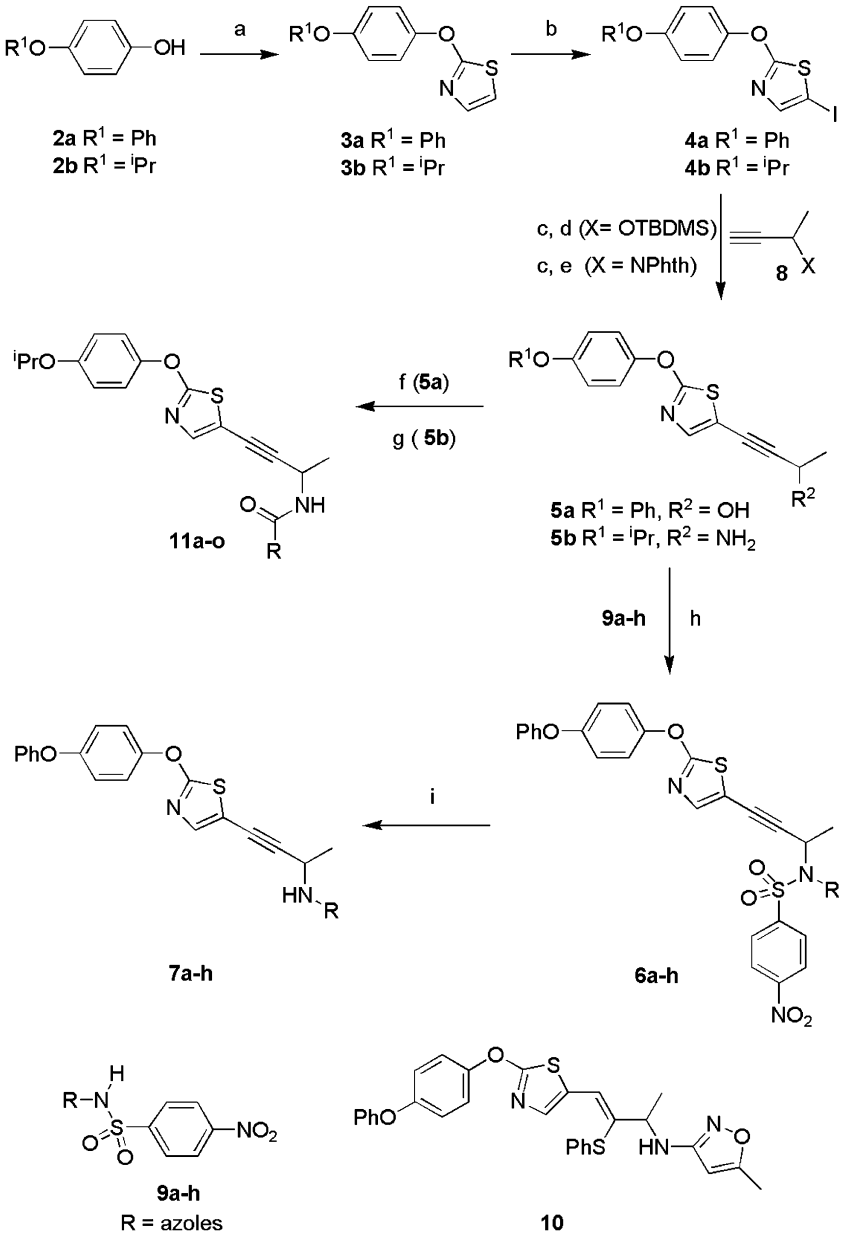
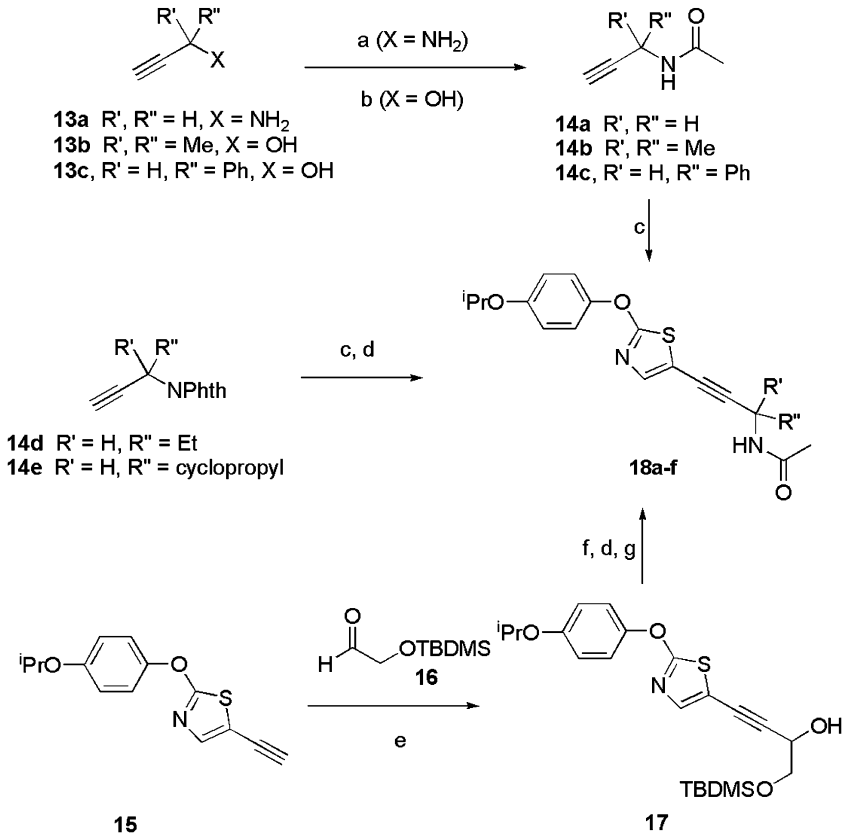


Scheme 1. Reagents and conditions: (a) 2-bromothiazole (1 equiv), K_2CO_3 (1.2 equiv), DMSO, 160 °C, 4 h, 63–74%; (b) BuLi (1.2 equiv), THF −78 °C, then I_2, 84–95%; (c) **8** (1 equiv), $Pd(Ph_3P)_2Cl_2$ (5%), CuI (2%), Et_3N (5 equiv), CH_3CN, 80 °C, 90%; (d) TBAF (1.5 equiv), THF, rt, 0.5 h, 76%; (e) NH_2NH_2 (10 equiv), CH_2Cl_2/EtOH (10:1), reflux, 3 h; (f) i—*p*-nitrophenyl chloroformate (1.1 equiv), pyridine (10 equiv), CH_2Cl_2, rt, 90%; ii—amines (2 equiv), Et_3N (excess), CH_3CN, rt or reflux; (g) acylation using anhydrides, acid chlorides, carbamoyl chlorides, and acids (or urea formation using isocyanates) followed by deprotection or hydrolysis; (h) **9a**–**h** (1.0 equiv), Ph_3P (1.5 equiv), DEAD (1.5 equiv), THF, rt, 12 h 26–63%; (i) PhSH (1.2 equiv), K_2CO_3 (4.0 equiv), DMF, rt, 2 h, 69–96%.

The general synthesis of **7a**–**h** and **11a**–**o** is outlined in Scheme 1. Displacement of 2-bromothiazole with 4-phenoxyphenol in the presence of potassium carbonate at 160 °C afforded the desired ether **3a**. Lithiation of **3a** followed by iodination provided **4a** as a single regioisomer. Sonogashira coupling[15] with TBDMS-protected 3-butyn-2-ol followed by deprotection gave product **5a** in 68% yield. Mitsunobu[16] reaction of **5a** with Boc-protected aminoazoles did not produce the desired heterocyclic products in satisfactory yield. For example, the reaction with 3-aminoisoxazole provided only 10% of isolated product after 2 days. Therefore, we utilized the Fukuyama methodology as a more practical synthesis of compounds **7a**–**h**.[17] The reaction between the various commercially available aminoazoles and 4-nitrophenylsulfonyl chloride afforded sulfonamide intermediates **9a**–**h**, which were successfully converted to **6a**–**h** via Mitsunobu reaction with **5a**. Deprotection of **6** with one equivalent of thiophenol in the presence of potassium carbonate afforded the desired products **7a**–**h** in very good yields (69–96%). Conditions employing excess thiophenol were found to exclusively produce acetylene addition product such as **10**. Compounds **11a**–**o** were prepared from **5b** as reported previously.[13]



Scheme 2. Reagents and conditions: (a) Ac_2O (1.1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C to rt, 70%; (b) Na_2SO_4 (1 equiv), H_2SO_4 (5 equiv), CH_2CN, −20 °C to rt, 50–74%; (c) **4b** (1 equiv), $Pd(Ph_3P)_2Cl_2$ (5%), CuI (2%), Et_3N (5 equiv), CH_3CN or THF, rt or reflux, 23–97%; (d) i—NH_2NH_2 (10 equiv), CH_2Cl_2/EtOH (10:1), reflux, 3 h; ii—Ac_2O (excess), Et_3N (excess), CH_2Cl_2; (e) BuLi (1.2 equiv), THF, −78 °C, 47%; (f) phthalimide (1.2 equiv), Ph_3P (1.5 equiv), DEAD (1.5 equiv), THF, rt, (37–94%); (g) AcOH/THF/water (3:1:1), rt, 92%.

Compounds with modifications at the α-position of the alkyne (**18a**–**f**) were synthesized from **14a**–**e** and **17** as depicted in Scheme 2. Compound **14a** was made by direct acylation of the amine, while **14b** and **14c** were prepared by the Ritter reaction[18] with the corresponding alcohols. Compound **18d** was synthesized by conversion of pentyn-3-ol to the corresponding phthalimidoyl-protected amine **14d** and subsequent coupling with **4b** followed by deprotection and acylation. Compounds **18e** and **18f** were synthesized in a similar way starting from **14e**[19] and **17**, respectively. The latter was prepared from TBDMS-protected hydroxyacetaldehyde **16** and alkyne **15**.

The SAR results on the polar region of **1** are summarized in Table 1. The cyclic aminoazoles **7a**–**h** in Table 1 were initially investigated as hydroxyurea replacements of HTS hit **1**. These compounds are comprised of varying polarities, hydrogen bond properties, and steric features. It is interesting that all of the aminoazoles exhibit significantly less potency for the ACC1 isoform. The ACC2 data for **7a**–**h** portrays a compact pocket that tolerates neither large groups, as exemplified by benzothiazole **7b** (IC_{50} >30 μM), nor polar aminoazoles such as imidazole **7d** (IC_{50} of 3.98 μM). Only the relatively small and lipophilic isoxazole analogs (**7c** and **7e**–**g**, IC_{50}s of 0.042, 0.083, 0.057, and 0.038 μM, respectively) retain the ACC2 potency of the parent hydroxyurea **1**. Yet, polarity and size do not entirely explain the SAR as demonstrated by the lipophilic and small thiazole **7a** (IC_{50} of 0.69 μM), which is 16-fold less potent than **7c**. It appears that the ring oxygen or the oxygen–nitrogen bond of the isoxazoles favorably interacts with the ACC2 binding pocket. Overall, aminoisoxazoles **7c** and **7e**–**g** provide potent and selective ACC2 inhibition and therefore serve as effective hydroxyurea replacements.

Further SAR investigations of the polar region proceeded with the isopropoxy group in the lipophilic region of the molecule since it has been shown to provide superior selectivity and potency for ACC2 compared to other phenyl ether replacements.[14] Small amides (**11a**) and carbamates (**11b**) are potent and selective ACC2 inhibitors as discussed before (IC_{50}s of 0.019 and 0.096 μM, respectively).[13] Similar potency and selectivity profiles are achieved when small urea groups are introduced (**11c**–**e**). The ACC2 potencies of methyl and dimethyl urea derivatives **11d** and **11e**, respectively, are similar to that of the parent unsubstituted analog (**11c**). However, as the substituents on the terminal urea nitrogen grow larger the potency decreases. Bulky urea analogs **11g** and **11j** are roughly 20-fold less potent than **11c**, while **11i**, with an IC_{50} of 20 μM, is relatively inactive. Similar to the urea series, increasing the amide size leads to diminished ACC2 potency as demonstrated by the

Table 1. Human ACC enzymatic activity for compounds **1**, **7a–h**, **11a–o**, and **18a–f**[a]

Compound	R	R′	R″	ACC1 IC_{50} (μM)	ACC2 IC_{50} (μM)
1				1.00	0.075
7a	2-Thiazolyl			10.68	0.69
7b	2-Benzothiazolyl			>30	>30
7c	3-Isoxazolyl			5.02	0.042
7d	2-Imidazolyl			>30	3.98
7e	5-Methyl-3-isoxazolyl			>30	0.083
7f	3-Methyl-5-isoxazolyl			>30	0.057
7g	3,4-Dimethyl-5-isoxazolyl			>30	0.038
7h	1-Ethyl-3-pyrazolyl			>30	0.44
11a	Me			>30	0.019
11b	OMe			>30	0.096
11c	NH_2			>30	0.037
11d	NHMe			>30	0.032
11e	$N(Me)_2$			>30	0.071
11f	NHOH			>30	0.33
11g	4-Morpholinyl			>30	0.67
11h	ONH_2			>30	0.68
11i	NHO^tBu			>30	20.49
11j	$NHCH_2CONH_2$			>30	0.92
11k	CO_2Me			>30	0.85
11l	CO_2H			>30	>30
11m	Cyclopentyl			>30	0.57
11n	3-Tetrahydrofuranyl			>30	0.22
11o	(S)-2-Pyrrolidinyl			>30	>30
18a		H	H	>30	1.86
18b		Me	Me	>30	0.50
18c		H	Ph	>30	>30
18d		H	Et	>30	0.53
18e		H	Cyclopropyl	>30	0.88
18f		H	CH_2OH	>30	0.91

[a] Enzymatic inhibition values of recombinant human ACC1 and ACC2, which were determined by measuring the incorporation of ACC-mediated [^{14}C] CO_2 into malonyl-CoA.

methyloxalate (**11k**), cyclopentyl (**11m**), and 3-tetrahydrofuranyl (**11n**) analogs (ACC2 IC_{50}s of 0.85, 0.57, and 0.22 μM, respectively) which are significantly less potent than **11a**. The polar and small hydroxylamine **11h** and hydroxyurea **11f** (ACC2 IC_{50}s of 0.68 and 0.33 μM, respectively) are weaker than **11b** and **11c**, respectively, suggesting that added polarity is not favorable. Moreover, introducing acidic (**11l**) or basic (**11o**) groups sharply decreases ACC2 activity (IC_{50}s of >30 μM). Consistent with the aminoazoles, the SAR in this region suggests a compact binding pocket that neither tolerates ionic groups nor interacts significantly with polar functionalities.

The tolerance for substitution at the propargylic position of lead compound **11a** was also explored. Compared with **11a** (IC_{50} of 0.019 μM), both removal (**18a**) and addition (**18b**) of a methyl group at the α position of the alkyne cause significant drop in ACC2 potency (IC_{50}s of 1.86 and 0.5 μM, respectively). Furthermore, when the size is increased from methyl to ethyl (**18d**), cyclopropyl (**18e**), and phenyl (**18c**), the ACC2 potency correspondingly diminishes (IC_{50}s of 0.53, 0.88, and >30 μM, respectively). Introducing polar functionality such as a hydroxymethyl group (**18f**) produces only modest ACC2 potency (IC_{50} of 0.91 μM) which is in line with the activity for the similar-sized ethyl analog **18d**. Generally, changes at the propargylic position of **11a** have no effect on ACC1 inhibition.

Modifications of HTS hit **1** have focused on the polar region. Aminoisoxazoles effectively replace the hydroxyurea group of **1**, maintain its ACC2 potency, and achieve a very good level of selectivity against ACC1 (>1000). SAR findings for aminoazoles and other amide-like hydroxyurea replacements demonstrate a lipophilic and compact binding pocket that does not tolerate polar or ionic interactions. Compared to the monomethyl group, all variations at the propargylic position decreased ACC2 potency.

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