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Design, synthesis and biological evaluation of novel spiro-pentacylamides as acetyl-CoA carboxylase inhibitors

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ABSTRACT

Acetyl-CoA carboxylase (ACC) catalyzes the rate-determining step in de novo lipogenesis and plays an important role in the regulation of fatty acid oxidation. Therefore, ACC inhibition offers a promising option for intervention in nonalcoholic fatty liver disease (NAFLD), type 2 diabetes (T2DM) and cancer. In this paper, a series of spiropentacylamide derivatives were synthesized and evaluated for their ACC1/2 inhibitory activities and anti-proliferation effects on A549, H1975, HCT116, SW620 and Caco-2 cell lines in vitro. Compound **6o** displayed potent ACC1/2 inhibitory activity (ACC1 IC_{50} = 0.527 μM, ACC2 IC_{50} = 0.397 μM) and the most potent anti-proliferation activities against A549, H1975, HCT116, SW620 and Caco-2 cell lines, with IC_{50} values of 1.92 μM, 0.38 μM, 1.22 μM, 2.05 μM and 5.42 μM respectively. Further molecular docking studies revealed that compound **6o** maintained hydrogen bonds between the two carbonyls and protein backbone NHs (Glu-B2026 and Gly-B1958). These results indicate that compound **6o** is a promising ACC1/2 inhibitor for the potent treatment of cancer.

1. Introduction

In contrast to normal differentiated cells, which satisfy their requirement for fatty acids by importing them from the circulation, cancer cells undergo high rates of de novo lipogenesis (DNL) to support cell division and continuous proliferation.[1,2] A wide number of cancers such as those of the prostate[3], hepatoma[4], bladder, lung, colon and ovary[5] have been shown to have a high rate of fatty acid synthesis (FASyn) which is reflected by the increased expression of lipogenic enzymes.[6–9] Modulation of lipogenic enzymes such as cytoplasmic acetyl-CoA synthetase (ACSS2)[10,11], ATP citrate lyase (ACLY)[12], acetyl-CoA carboxylase (ACC)[13–15]and fatty acid synthase (FASN)[16] have demonstrated inhibition of cell growth and proliferation in cancer models both in vitro and in vivo.

Acetyl-CoA carboxylase (ACC) is a biotin-dependent protein, composed of a carboxyl transferase domain (CT), biotin carboxy carrier protein (BCCP) and biotin carboxylase domain (BC), which catalyzes the ATP-dependent carboxylation of acetyl-CoA to form malonyl-CoA, the rate-limiting and first committed reaction in FASyn.[17,18] There are two characterized isoforms of mammalian ACC (known as ACC1 and ACC2), which are encoded by separate genes and display distinct cellular distributions.[19] ACC1 is located in the cytosol and primarily expressed in lipid rich tissues (liver, adipose).[20] In contrast, the second ACC isoform, ACC2 is a mitochondrially associated isozyme present in oxidative tissues (heart, skeletal muscle).[21] ACC1 converts acetyl-CoA into malonyl-CoA for DNL while the ACC2 isoform carries out the same reaction to generate malonyl-CoA for the inhibition of carnitine palmitoyl transferase 1 (CPT-1)[22], the protein that catalyzes the conjugation of free fatty acyls to carnitine from entering the mitochondrial membrane for subsequent β-oxidation.[23] Thus, malonyl-CoA production by ACC2 activity serves to directly inhibit fatty acid oxidation. Considering the roles of the ACC in both the synthesis and oxidation of fatty acids, inhibition of ACC1/2 has the potential to favorably affect a variety of metabolic diseases including T2DM, obesity and NAFLD by reducing lipid accumulation and improving insulin sensitization.[24,25] In addition, given that the tumor cells rely on FASyn for energy storage, membrane formation and production of signaling molecules[26] and that both ACC and FASN mRNAs are upregulated in a number of cancers, FASyn has been postulated to offer a therapeutic window. In this paper, efforts to target cancer cells that bear elevated rates of lipogenesis have focused on attempts to chemically inhibit ACC1/2.

To date, several classes of small molecule ACC1/2 inhibitors have been reported and the representative structures are presented in Fig. 1[5, 15, 27–29]. Pfizer has had a long-standing interest in the development of ACC inhibitors and reported a series of potent, nonselective and orally bioavailable spirochormanone

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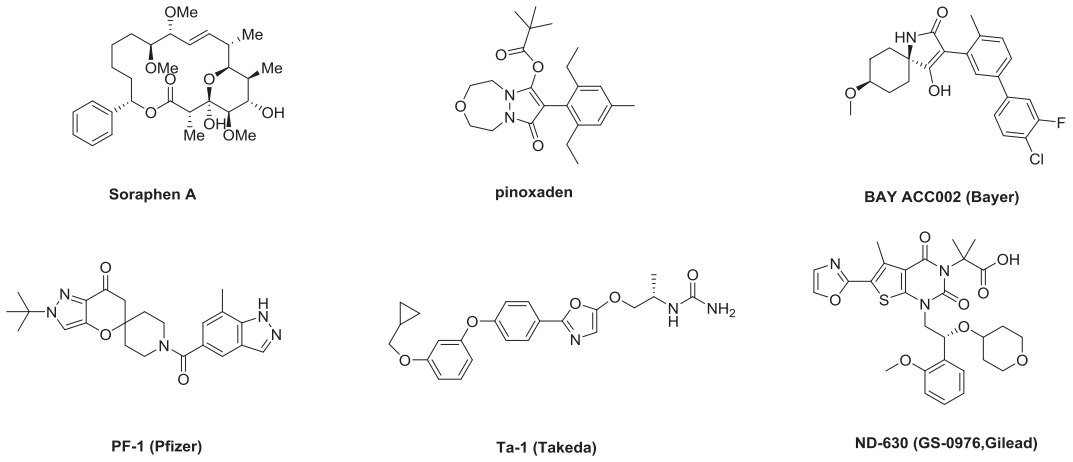

Fig. 1. Representative inhibitors of ACC.

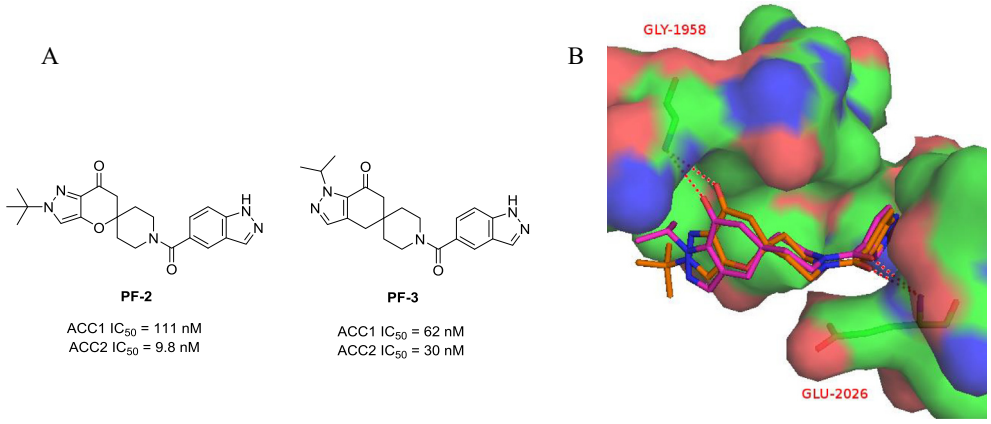

Fig. 2. (A). ACC inhibitors **PF-2** and **PF-3**. (B). Co-crystal structure of **PF-2** (orange) bound in the CT-domain of ACC, overlaid with the bound conformation of **PF-3** (magenta). PDB accession codes: **PF-2**, 4WYO; **PF-3**, 4WZ8.

ACC1/2 dual inhibitors as exemplified by **PF-1** and the co-crystal structure of the humanized yeast ACC carboxyl transferase (CT) domain in complex with **PF-2** was performed (PDB: 4WYO, Fig. 2). Compound **PF-2** was oriented in the channel generated at the dimeric interface of the N and C domains, and the pyrazolopyranone group was filling a narrow, deep, hydrophobic pocket formed by a cluster of hydrophobic residues (Leu-A1762, Val-A1765, Leu-A1766, Ala-B1920, Val-B1923, and Phe-B1925) from each domain. The co-crystal data also indicated that the amide carbonyl (right side) interacts with the backbone of Glu-B2026 and the ketone carbonyl (left side) is bound to the backbone of Gly-B1958, which made significant contributions to binding potency. Notably, further co-crystal structure published by Pfizer of compound **PF-3** (Fig. 2) demonstrated that the proper fixation of the ketone carbonyl (left side) direction may lead to a nearly identical hydrogen bonding interaction as compared to **PF-2**. In addition, the structural rigidity imparted by the spirocyclic ring system was essential to binding by reducing the entropic penalty for properly orienting the hydrogen bond acceptors.[30] Herein, we report the discovery of a spirolactam derivative **6o** bearing a spiropentacylamide ring formed by focusing interactions with Gly-B1958 and Glu-B2026 to explore inhibitory activity of ACC.

On the basis of spirochromanone scaffold reported by Pfizer, our modification strategy was focused on the pyrazolopyranone region of compound **PF-2** as shown in Fig. 3. Spatial orientation of the amide carbonyl (right side) and ketone carbonyl (left side) were retained to form the key hydrogen-bonds with Glu-B2026 and Gly-B1958, respectively. On the other hand, we focused on searching for substituents that would provide an optimal fit in the binding pocket composed primarily of hydrophobic side chains. In consideration of the above two points, the spiropentacylamide scaffold was designed. Meanwhile a range of phenyl substituents were introduced via standard Buchwald coupling conditions to occupy the hydrophobic pocket.

Herein, we would like to describe our efforts on the biological evaluation and structural optimization of the novel spiropentacylamide-based ACC1/2 inhibitors. The synthesized compounds were evaluated for their biological activities in vitro toward five different human tumor cell lines, and ACC enzymes. Among these derivatives, compound **6o** with the most potent ACC inhibition activity (ACC1 IC_{50} = 0.527 μM, ACC2 IC_{50} = 0.397 μM) and the most potent anti-proliferation activity against A549, H1975, HCT116, SW620 and Caco-2 cell lines (1.92 μM, 0.38 μM, 1.22 μM, 2.05 μM and 5.42 μM), respectively, was considered to be a promising lead compound worthy of further investigation. The binding interactions between ACC and compound **6o** are presented within this paper as well.

2. Chemistry

The synthetic route with high to moderate yields for accessing the desired compounds **6a**–**6t** is described in Scheme 1. The