ACS Medicinal Chemistry Letters

Patent Highlight

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Treatment of Obesity and Related Disorders with Acetyl-CoA Carboxylase Inhibitors

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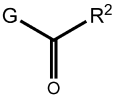
Title:	Pyrazolospiroketone Derivatives for Use as Acetyl-CoA Carboxylase Inhibitors		
Patent Application Number:	WO 2012/143813 A1	**Publication Date:**	October 26, 2012
Priority Application:	US 61/478,240	**Priority Date:**	April 22, 2011
Inventors:	Griffith, D. A.; Dow, R. L.; Southers, J. A., Jr.; Edmonds, D. J.		
Assignee Company:	Pfizer Inc., 235 East 42nd Street, New York, New York 10017, United States		
Disease Area:	Obesity and Obesity-Related Diseases (Such as, NAFLD and Type 2 Diabetes)	**Biological Target:**	Acetyl-CoA Carboxylases: ACC1 and ACC2

Summary:

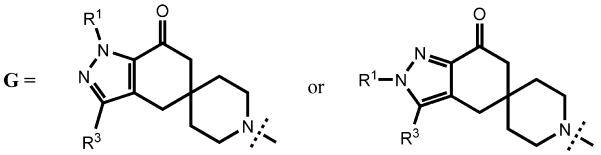
The invention in this patent application relates to pyrazolospiroketone derivatives represented by formula (I) that act as inhibitors of acetyl-CoA carboxylases (ACC); these inhibitors can potentially treat obesity and related diseases.

Acetyl-CoA carboxylases (ACC) regulate the biosynthesis and metabolism of fatty acids. They catalyze the carboxylation of acetyl-CoA to form malonyl-CoA, which is a building block for the biosynthesis of fatty acids. ACC1 and ACC2 are two main isoforms of ACC in mammals. ACC1 is expressed at high levels in lipogenic tissues and controls the regulation of long-chain fatty acids biosynthesis. ACC2 is the predominant isoform in heart and skeletal muscle; it regulates β-oxidation of fatty acids by inhibiting carnitine palmitoyl transferase. Studies have demonstrated that hepatic lipid accumulation causes hepatic insulin resistance and contributes to the pathogenesis of type 2 diabetes. In vivo studies have also shown that reduction of the two ACC isoforms (ACC1 and ACC2) is required to significantly reduce lipid accumulation and improve insulin action. The inhibition of ACC enzymes is thus a viable therapeutic target to treat obesity by increasing fatty acid oxidation and suppressing fatty acid synthesis, a combination that may lead to loss of body fat in obese subjects. The molecules introduced in this patent application and represented by Formula (I) act as inhibitors of ACC1 and/or ACC2 and may possibly provide a treatment for obesity and obesity-related diseases such as nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes.

Important Compound Classes:

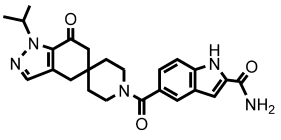


Formula (I)

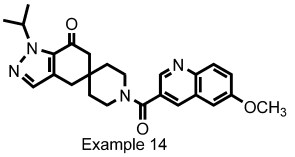


Key Structures:

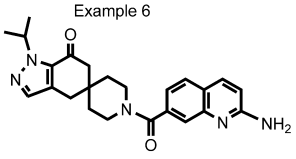
The application describes the synthesis of 73 examples. In addition to the general structure claims, 18 structures were claimed specifically by chemical names and three claimed by structure.



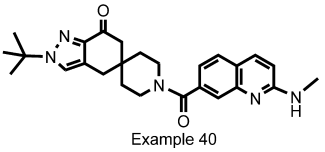
Example 6



Example 14



Example 25



Example 40

Biological Assay:

The direct inhibition of ACC activity by the compound of Formula (I) was determined using preparations of recombinant human ACC1 (rhACC1) and recombinant human ACC2 (rhACC2).

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Biological Data: The IC_{50} values were reported for 49 compounds; the following table contains results for the four representative examples shown above.

Example	hACC1 IC_{50} (nM)	n	hACC1 IC_{50} (nM)	n
6	11	4	2.9	4
14	5.0	5	2.1	5
25	12	2	10	1
40	2.2	3	1.3	3

Claims: Claims 1−6: Composition of matter, variations of Formula (I)
Claim 7: Composition of matter; a list of 18 compounds listed by chemical name
Claims 8−10: Composition of matter; three specific compounds listed by structures
Claim 11: Pharmaceutical composition
Claims 12−14: Use of compounds as medicament

Recent Review Articles:
1. Lenhard, J. M. *Curr. Pharm. Des.* **2011**, *17* (4), 325−331.
2. Schreurs, M.; Kuipers, F.; van der Leij, F. R. *Obes. Rev.* **2010**, *11* (5), 380−388.
3. Corbett, J. W. *Expert Opin. Ther. Pat.* **2009**, *19* (7), 943−956.
4. Folmes, C. D. L.; Lopaschuk, G. D. *Cardiovasc. Res.* **2007**, *73* (2), 278−287.

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Notes

The authors declare no competing financial interest.