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Viewpoint

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Fatty Acid Synthase Inhibitors as Possible Treatment for Cancer

Patent Highlight

Ahmed F. Abdel-Magid*

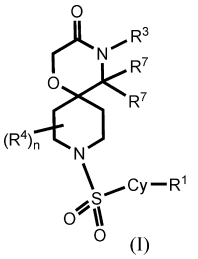
Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Title:	Fatty acid synthase inhibitors		
Patent Application Number:	WO2012/064642Al	**Publication date:**	May 24, 2012
Priority Application:	61/411,110	**Priority date:**	November 8, 2010, US
Inventors:	Adams, Nicholas D.; Chaudhari, Amita M.; Kiesow, Terence J.; Parrish, Cynthia Ann; Reif, Alexander J.; Ridgers, Lance H.; Schmidt, Stanley J.; Wiggall, Kenneth		
Assignee Company:	GlaxoSmithkline LLC, One Franklin Plaza, 200 North 16th Street, Philadelphia, Pennsylvania 19102, United States		
Disease Area:	Cancer	**Biological Target:**	Fatty Acid Synthase (FAS)

Summary:

The spirocyclic piperidines of formula (I) inhibit the function of fatty acid synthase (FAS). FAS is a multifunctional homodimeric enzyme protein, and it is the major enzyme required for the anabolic conversion of dietary carbohydrates to fatty acids. It synthesizes long-chain fatty acids by using acetyl-CoA as a primer, malonyl Co-A as a 2 carbon donor, and NADPH for reduction. The normal level of activity of FAS in adult cells is very low, as most normal human tissues preferentially acquire fatty acids from dietary sources. However, many cancer tumor cells have shown high rates of fatty acid synthesis and overexpression of FAS in numerous cancer types including prostate, ovary, colon, endometrium, lung, bladder, stomach, and kidney. This variance in the levels of FAS in tumors versus normal cells suggests a potential link between increased FAS expression and increased risk of cancer. Controlling FAS levels may provide some means of cancer therapy and makes inhibition of FAS a major potential target in cancer treatment. The claimed compounds of formula (I) described in this patent application as inhibitors of FAS may be used for treating cancer in humans.

Important Compound Classes:

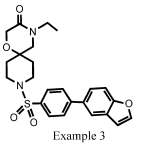


(I)

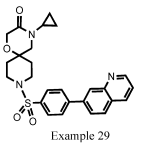
Cy represents optionally substituted aryl and heteroaryl rings such as Phenyl, Pryridinyl and 5- or 6-membered heteroaryl groups

Key Structures:

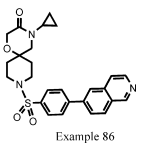
The syntheses of 146 examples of the compounds of formula (I) are described in the experimental section. The following are three structural examples:



Example 3



Example 29



Example 86

Biological Assay:

FAS activity was measured through one of the two following assays:

1. The detection of residual NADPH substrate after the FAS assay is quenched
2. The detection of the CoA products with a thio-reactive coumarin dye

Biological Data:

Examples were tested for FAS inhibition. The IC_{50} values ranged from about 1 nM to about 10 mM. The IC_{50} values of the more active compounds range from about 1 to about 200 nM. The most active compounds are under 10 nM. The average IC_{50} values of some of the examples are listed in the table below:

Example No.	IC_{50} (nM)
Example 3	251
Example 13	1259
Example 14	40
Example 26	200
Example 29	10
Example 59	13
Example 70	32
Example 76	32
Example 86	6
Example 105	63

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Claims:	Claims 1−12: composition of matter; variations of formula I
	Claim 13: composition of matter; 146 examples of the compounds of formula (I) are claimed specifically by name
	Claim 14: a pharmaceutical composition
	Claims 15−18: method for treating cancer
Recent Review Articles:	Pandey, P. R.; Liu, W.; Xing, F.; Fukuda, K.; Watabe, K. Anticancer drugs targeting fatty acid synthase (FAS). *Recent Pat. Anticancer Drug Discovery* **2012**, *7* (2), 185−197.
	Tian, W.-x.; Ma, X.-f.; Zhang, S.-y.; Sun, Y.-h.; Li, B.-h. Fatty acid synthase inhibitors from plants and their potential application in the prevention of metabolic syndrome. *Clin. Oncol. Cancer Res.* **2011**, *8* (1), 1−9.
	Wang, C.; Rajput, S.; Watabe, K.; Liao, D.-F.; Cao, D. Acetyl-CoA carboxylase-α as a novel target for cancer therapy. *Front. Biosci., Scholar Ed.* **2010**, *S2* (2), 515−526.
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	Lupu, R.; Menendez, J. A. Pharmacological inhibitors of Fatty Acid Synthase (FASN)-catalyzed endogenous fatty acid biogenesis: A new family of anticancer agents? *Curr. Pharm. Biotechnol.* **2006**, *7* (6), 483−493.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania, 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.