# ACS Medicinal Chemistry Letters

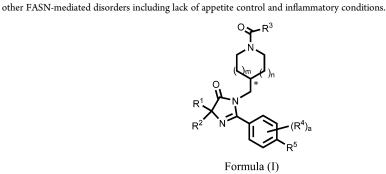
# Fatty Acid Synthase (FASN) Inhibitors as Potential Treatment for Cancer, Obesity, and Liver Related Disorders

Ahmed F. Abdel-Magid\*

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

Title:	Imidazolin-5-one Derivative Useful as FASN Inhibitors for the Treatment of Cancer					
Patent Application Number:	WO 2015/095011 A1	Publication date:	25 June 2015			
Priority Application:	US 61/916,844	Priority date:	17 December 2013			
Inventors:	Connolly, P. J.; Lu, T.					
Assignee Company:	Janssen Pharmaceutica NV; Turnhoutseweg 30, B-2340 Beerse (BE)					
Disease Area:	Cancer, obesity related disorders, and liver related disorders	<b>Biological Target:</b>	Fatty acid synthase (FASN)			
Summary:	<ul> <li>The invention is in this patent application relates to 1<i>H</i>-imidazol-5(4<i>H</i>)-one derivatives represented generally by formula (I). These compounds are FASN inhibitors and may potentially provide treatments for cancer, obesity related disorders, and liver related disorders.</li> <li>Fatty acid synthase (FASN) is a 250 kDa protein that contains seven functional domains; it is a key enzyme in the de novo synthesis of long-chain fatty acids starting with acetyl-coenzyme A (CoA) and malonyl-CoA using NADPH as a reducing cofactor. FASN is highly expressed in lipogenic tissues such as liver, lactating breast, fetal lung, and adipose tissue, but it is minimally expressed in most normal human tissues. The low level of FASN expression in normal cells occurs because these cells obtain their needed fatty acids from diet rather than from lipogenesis. It was discovered that the expression of FASN is highly up-regulated in</li> </ul>					
	in the growth and survival of the tumors through multiple mec increased saturated lipid content in the membranes increase	ancer. The overexpression of FASN in tumor cells is believed to aid chanisms. FASN provides saturated lipids for membrane synthesis; es their resistance to chemotherapy. It also helps in improving oving cell signaling. In addition, the consumption of NAPDPH due neck.				
	Studies using siRNA knock down or pharmacological inhibition of tumor growth in vivo. Other studies using transgenic mouse mo of FASN as a potential oncogene. The results of many studies ha intrinsic pathway of apoptosis. FASN expression and activities a overexpressed in androgen-independent prostate cancers prob The above data point to the importance of the inhibition of FASN lead to the development of new effective treatment for cancer application may potentially provide needed therapeutics for the implicated in diabetes and/or regulation of the general wellness	FASN in tumor cells have re odels with FASN overexpres we suggested that FASN exe re up-regulated by androger ably through activation of t activities as an emerging an FASN inhibitors such as t e treatment of several forms	ssion in the prostate established the role erts its oncogenic effect by inhibiting the ns and epidermal growth factor. It is also the PI3K/Akt pathway. d promising therapeutic target that may he compounds described in this patent s of cancer. In addition, FASN has been			

Important Compound Classes:



treatments for obesity, type II diabetes mellitus, syndrome X, and disorders of the liver. They may also be useful as treatments for

 Received:
 July 8, 2015

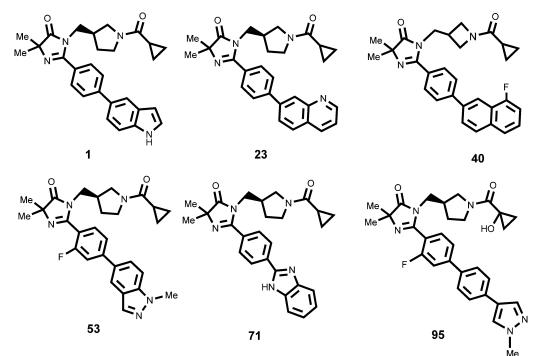
 Published:
 July 15, 2015



ACS Publications © 2015 American Chemical Society

#### **Key Structures:**

The inventors reported the structures of 99 compounds representing examples of formula (I) including the following compounds:



#### **Biological Assay:**

The inventors described the following biological assays to test formula (I) compounds:

- 1. Fatty Acid Synthase (FASN) Inhibition Scintillation Proximity Assay
- 2. Fatty Acid Synthase Keto-reductase Domain (FASN KR) Inhibition
- 3. A2780 ovarian cell proliferation assay in lipid reduced medium, with and without palmitate
- 4. (a)in vitro LNCaP Vancouver prostate cell proliferation assay in lipid reduced medium; (b) in vitro PC-3M-Luc-C6 prostate cell proliferation assay in lipid reduced medium
- 5. Prophetic Example 14C~acetate Incorporation in HEPG2 Liver Cells
- 6. Prophetic Example Analysis of Intact Phospholipid Species by Electrospray Ionization Tandem Mass Spectrometry
- 7. Prophetic Example Xenograft Hematological Assay
- 8. In vivo MaCoA determination in NCI-H460 xenografts

**Biological Data:** 

The reported assay results from testing the representative examples (see structures above) using assays 1-4 are listed in the following table:

Compound	ScintillationKeto- reductaseProximityreductaseAssayDomain $(plC_{50})$ $(plC_{50})$ $(plC_{50})$		Ovarian cell, reduced medium		prostate cell proliferation assay, reduced medium	
		With palmitate	Without palmitate	LNCaP Vancouver	PC-3M- Luc-C6	
	(prC <sub>50</sub> )	(prC <sub>50</sub> )	(pIC <sub>50</sub> )	(pIC <sub>50</sub> )	(pIC <sub>50</sub> )	(pIC <sub>50</sub> )
1	7.32	6.86	<5	7.13		
23	7.25	7.25	<5	7.12	6.66	7.27
40	6.75	6.46	5.25	6.33	5.69	
53	7.03	6.49			6.14	6.88
71	5.23		<5	~5.03		
95	7.52		<5	~8.27		

**Recent Review Articles:** 

1. Wu, X.; Qin, L.; Fako, V.; Zhang, J.-T. Adv. Biol. Regul. 2014, 54, 214-221. 2. Maruyama, T.; Murata, S.; Ohkohchi, N. Horiz. Cancer Res. 2012, 49, 153-177.

3. Pandey, P. R.; Liu, W.; Xing, F.; Fukuda, K.; Watabe, K. Recent Pat. Anticancer Drug Discovery 2012, 7 (2), 185-197. 4. Liu, H.; Liu, J.-Y.; Wu, X.; Zhang, J.-T. Int. J. Biochem. Mol. Biol. 2010, 1 (1), 69-89.

# 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.