ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

pubs.acs.org/acsmedchemlett

Fighting Obesity and Metabolic Disorders with DGAT-1 Inhibitors

Ahmed F. Abdel-Magid*

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

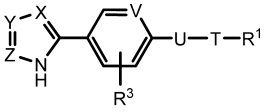
Patent Application Title:	Compounds as DGAT-1 Inhibitors		
Patent Application Number:	WO 2013/096093 Al	**Publication date:**	27 June 2013
Priority Application:	US 61/578,288	**Priority date:**	21 December 2011
Inventors:	Devita, R. J.; He, S.; Liu, J.; Cernak, T. A.; Krikorian, A. D.; Yang, G. X.; Wu, Z.; Yu, Y.; Shen, D.-M.; Lai, Z.; Hong, Q.; Nargund, R. P.		
Assignee Company:	Merck Sharp & Dohme Corp.; 126 East Lincoln Avenue, Rahway, New Jersey 07065−0907, United States		
Disease Area:	Obesity, hyperlipidemia, and diabetes mellitus	**Biological Target:**	Diacylglycerol acyltransferase-1 (DGAT-1)

Summary: The invention in this patent application introduces imidazole derivatives represented generally by formula (I), which are DGAT-1 inhibitors and may potentially be useful for the treatment of obesity, hyperlipidemia, and diabetes mellitus.

A major cause of obesity is the accumulation of triglycerides (TG) in adipose tissue. Dietary TG are hydrolyzed with pancreatic lipase to 2-monoacylglycerol and fatty acids, which are absorbed by intestinal epithelial enterocytes. These hydrolysis products are then used to resynthesize triglycerides through the monoacylglycerol pathway in the small intestine. This pathway includes two sequential acylation steps; the first is catalyzed by monoacylglycerol acyltransferases (MGATs), and the second is catalyzed by diacylglycerol acyltransferases (DGATs). Another pathway is glycerol 3-phosphate pathway, which is a de novo pathway that is present in most tissues.

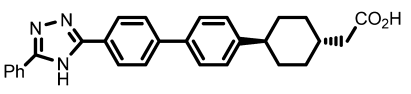
Diacylglycerol acyltransferases (DGATs) that catalyze the final step of the TG synthesis contain two subtypes, DGAT-1 and DGAT-2. The two isozymes catalyze similar reactions but have no significant homology to each other. DGAT-1 is present in the small intestine, adipose tissue, and liver. It is believed to play a role in lipid absorption and accumulation in the fat cells and in the liver. Studies on genetically modified mice as well as pharmacological data suggest that inhibition of DGAT-1 is a promising target for the treatment of obesity and type-2 diabetes. Thus, DGAT-1 inhibitors such as the compounds in this patent application may potentially provide effective treatment for obesity and other metabolic disorders.

Important Compound Classes:

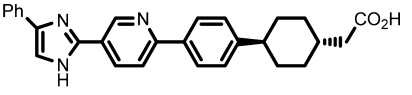


Formula (I)

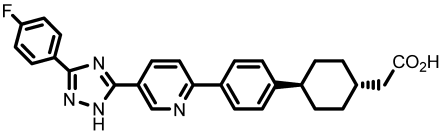
Key Structures: The inventors report the synthesis procedures and structures of 182 examples of the compounds of formula (I) including the following four examples:



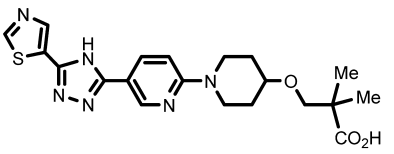
Example **1**



Example **16**



Example **21**



Example **72**

Received: July 15, 2013
Published: August 08, 2013

Biological Assay: DGAT1 CPM Assay

Biological Data: The inventors report the IC_{50} values for the 182 examples; the values for the above four compounds are listed in the table (the concentrations were not specified for IC_{50})

Compound	h-DGAT-1 IC_{50}	Compound	h-DGAT-1 IC_{50}
Example **1**	5.833	Example **16**	4.838
Example **21**	1.902	Example **72**	4856

Claims: Claims 1−16: Composition of matter; variations of formula (I)
Claim 17: 182 specific examples of formula (I) listed by chemical structures
Claims 18: Pharmaceutical compositions
Claims 19−21: Use of compounds as treatments

Recent Review Articles:
1. Schober, G.; Arnold, M.; Birtles, S.; Buckett, L. K.; Pacheco-Lopez, G.; Turnbull, A. V.; Langhans, W.; Mansouri, A. *J. Lipid Res.* **2013**, *54* (5), 1369−1384.
2. Stienstra, R.; Kersten, S. *J. Lipid Res.* **2011**, *52* (4), 591−592.
3. Birch, A. M.; Buckett, L. K.; Turnbull, A. V. *Curr. Opin. Drug Discovery* **2010**, *13* (4), 489−496.

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.