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PATENT HIGHLIGHT

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Fighting Obesity and Metabolic Disorders with MGAT-2 Inhibitors

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Patent Application Title:	Aryl Dihydropyridinones and Piperidinones as MGAT2 Inhibitors		
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Priority Application:	US 61/566,039	**Priority date:**	2 December 2011
	US 13/688,584		29 November 2012
Inventors:	Turdi, H.; Hangeland, J. J.; Lawrence, R. M.; Cheng, D.; Ahmad, S.; Meng, W.; Brigance, R. P.; Devasthale, P.		
Assignee Company:	Bristol−Myers Squibb Company, P.O. Box 4000, Route 206 and Province Line Road, Princeton, New Jersey 08543−4000, United States		
Disease Area:	Obesity, type II diabetes, dyslipidemia, and related conditions **Biological Target:** Monoacylglycerol acyltransferase-2 (MGAT2)		

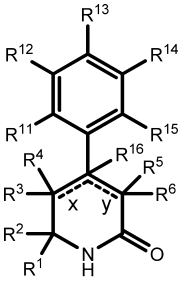
Summary:

The invention in this patent application introduces novel aryl dihydropyridinone and piperidinone compounds represented generally by formula (I), which are MGAT2 inhibitors and may potentially be used for the treatment or prophylaxis of diabetes, obesity, dyslipidemia, and related conditions.

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.

Monoacylglycerol acyltransferase-2 (MGAT2), one of the enzymes that catalyzes the first step, is highly expressed in the small intestine. It has emerged as an attractive target for the treatment of obesity and type II diabetes. Studies have shown that MGAT2 knockout mice exhibit healthy metabolic phenotype and better resistance to high-fat diet induced obesity as well as decreased fat accumulation in liver and adipose tissue. Therefore, MGAT2 inhibitors such as the compounds described in this patent application may potentially provide an effective treatment for metabolic disorders such as obesity, type II diabetes, and dyslipidemia.

Important Compound Classes:



Formula (I)

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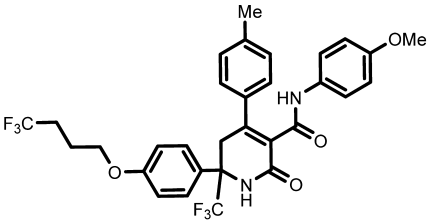
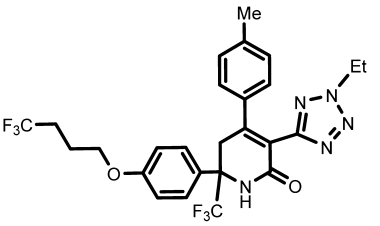
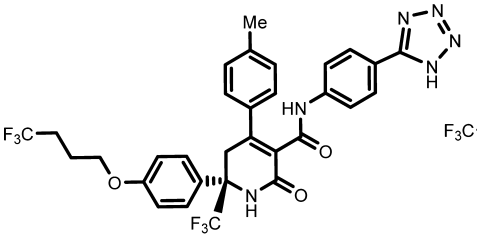
Key Structures: The inventors disclose 314 examples of formula (I) compounds including the following compounds:



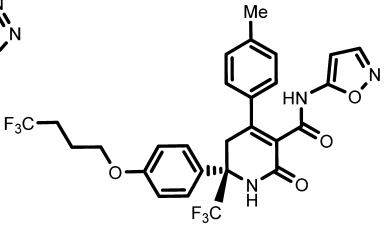
Example **6**



Example **9**



Example **111**



Example **167**

Biological Assay:

- MGAT SPA Assay
- MGAT LCMS Assay

Biological Data: The inventors report the IC_{50} values from one or both assays for 314 examples; the values for the above four structures are listed in the table:

Compound	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
Example **6**	15	7
Example **9**	33330	121
Example **111**	9	7
Example **167**	8	2

Claims: Claims 1−9: Composition of matter; variations of formula (I)
Claim 10: 20 specific examples of formula (I) listed by chemical names
Claims 11−13: Pharmaceutical compositions
Claims 14−15: Use of compounds as treatments

Recent Review Articles:
1. Cao, G.; Konrad, R. J.; Li, S. D.; Hammond, C. *Endocr., Metab. Immune Disord.: Drug Targets* **2012**, *12* (2), 197−206.
2. Wang, Y.; Schachter, H.; Marth, J. D. *Biochim. Biophys. Acta, Gen. Subj.* **2002**, *1573* (3), 301−311.

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Notes

The authors declare no competing financial interest.