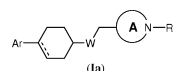


Modulators of the GPR119 Receptor for the Treatment of Metabolic Syndrome

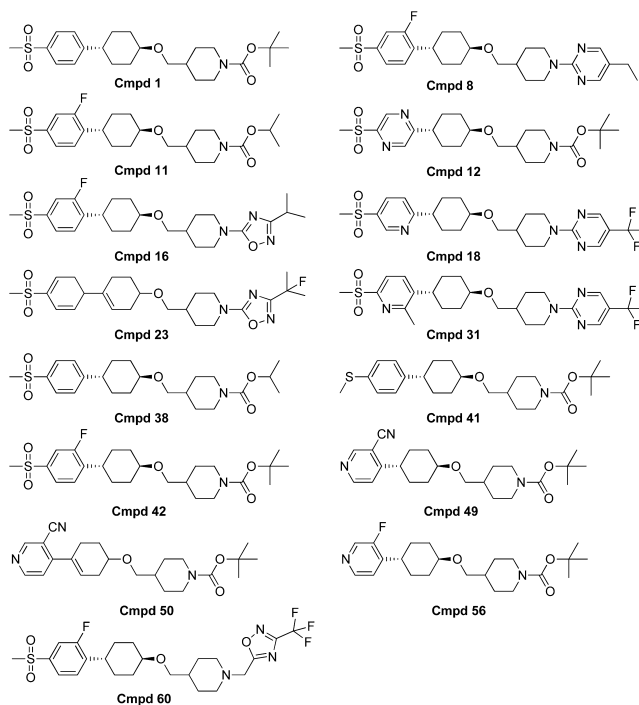
Gerard Rosse*,†

Structure Guided Chemistry, Dart Neuroscience LLC, 7473 Lusk Boulevard, San Diego, California 92121, United States

Title:	Modulators of the GPR119 Receptor for the Treatment of Metabolic Syndrome		
Patent/Patent Application Number:	WO 2012135570 A1	Publication Date:	October 4, 2012
Priority Application:	US 2011-470792P	Priority Date:	April 1, 2011
Inventors:	Jones, R. M.; Han, S.; Lehmann, J.; Thoresen, L.		
Assignee Company:	Arena Pharmaceuticals, Inc., United States		
Disease Area:	Metabolic-Related Disorder	Biological Target:	GPR119 Receptor
Summary:	The patent application claims agonists of GPR119 for the treatment of type 2 diabetes and obesity.		
Important Compound Classes:			

**Definitions:**W = CH₂, O, S(O)_m, NR²

A = substituted piperidin-4-yl, 3-azabicyclo[3.2.1]octan-8-yl and 8-azabicyclo[3.2.1]octan-8-yl

Key Structures:**Biological Assays:**

GPR119 agonists were evaluated in an HTRF cAMP detection assay. Selected compounds were tested in vivo for their effect (i) on incretin hormone GIP release and (ii) on glucose homeostasis.

Received: November 15, 2012

Published: November 27, 2012

Pharmacological Data:

HTRF cAMP detection assay

Cmpd	EC ₅₀ hGPR119 (nM)	Cmpd	EC ₅₀ hGPR119 (nM)
1	16	38	57
11	21	41	505
12	707	42	6.4
16	38	49	1030
18	134	50	38
23	15	56	63
31	42	60	200

In vivo effects of compound 8 on Glucose homeostasis

Time Relative to Glucose Bolus (min)	20% HPCD			Compound 8 (3 mpk)			Compound 8 (30 mpk)		
	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n
-30	77.7	5.011	6	88.7	7.274	6	72.2	3.936	6
0	100.8	7.485	6	112.5	12.076	6	96.0	5.767	6
20	233.0	30.245	6	201.3	10.101	6	163.5	23.284	6
40	309.0	32.820	6	250.2	23.331	6	204.2	27.950	6
60	343.5	35.423	6	262.8	28.051	6	193.2	24.105	6
120	176.7	10.025	6	163.3	20.172	6	107.5	9.999	6

Compound 8 is an agonist in an incretin hormone GIP release assay, and at a dose of 4 mg/kg po, it stimulates the release of GIP.

Claims:

Claim S1: Use of compounds for the treatment of varied diseases including, for example, metabolic-related disorders, obesity, cardiovascular disease, metabolic syndrome, neurodegenerative disorder, memory impairment, prion-associated disease, motor-neuron disease, Huntington's disease, Alzheimer's disease, and Parkinson's disease

Claim S2: Use of compounds for the treatment of type 2 diabetes

Claims S3 and S4: Use of compound of the invention in combination with a DPP-IV, a biguanidine, or an α glucosidase inhibitor

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: grosse@dartneuroscience.com.

Present address

†Adjunct Associate Professor, Department of Pharmacology and Physiology, Drexel University, College of Medicine, New College Building, 245 N. 15th Street, Philadelphia, PA 19102.

Notes

The authors declare no competing financial interest.