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GPR119 Modulators for the Treatment of Diabetes, Obesity, and Related Diseases

Patent Highlight

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GPR119 Modulators for the Treatment of Diabetes, Obesity and Related Diseases

General Background:

Diabetes mellitus (commonly called diabetes) is a metabolic disease that causes the elevation of blood sugar in patients. Diabetes mellitus type 1 makes up <10% of all diabetes cases and results from insulin deficiency due to destruction of islet cells in the pancreas. Diabetes mellitus type 2 is the most common, and it makes up about 90% of all cases of diabetes; it results from insulin resistance and relative insulin deficiency (may be due to reduced numbers of cellular insulin receptors, disruption of cellular signaling pathways, or both). Gestational diabetes is a temporary form of diabetes that occurs in some pregnant women who are not previously diagnosed with diabetes. The 2011 World Health Organization (WHO) data show that type 2 diabetes (T2D) affects >346 million patients worldwide. According to the American Diabetes Association 2011 statistics, there are >25 million patients in the United States, including 7 million undiagnosed cases in addition to nearly 79 million cases of prediabetes. Long-term complications from high blood sugar include heart disease; strokes; diabetic retinopathy, where eyesight is affected; kidney failure, which may require dialysis; and poor circulation of limbs, leading to amputations.

Obesity is thought to be one of the primary causes of T2D in people who are genetically prone to the disease. It usually results from increased calorie intake versus energy consumption. Obesity significantly increases the risk of the development of cardiovascular diseases, and it is estimated that about 20% of the obese population will become diabetic. While obesity is considered a critical risk factor for diabetes, it is still unknown how the accumulation of fat in some patients affects a pathological change in insulin secretion.

Currently, there is no cure for diabetes. T2D is initially managed by regular exercise and dietary modification; then, as it progresses, it is managed by medications and/or insulin. Standard medications for the disease focus on controlling blood glucose levels. Each medicine can be taken alone or in combination with others or with insulin. Diabetes medications are classified into several groups; some of the main classes are as follows:

1. **Biguanides**: Biguanidine structures act by activating the enzyme AMP-activated protein kinase (AMPK) that plays a role in insulin signaling and metabolism of glucose and fat. For example, metformin (a.k.a. glucophage) is the most used T2D medication.

2. **Sulfonylureas**: Insulin secretagogues act by inhibiting the K_{ATP} channel of the pancreatic β-cells. An example is glimepiride (Amaryl); drugs in this class may induce hypoglycemia, weight gain, and increased risk of cardiovascular death.

3. **Thiazolidinediones**: These act by binding to the regulatory protein PPARγ, which regulates fatty acid storage and glucose metabolism. Examples are rosiglitazone (Avendia) and pioglitazone (Actos); there are some studies that link some of these drugs with an increased risk of heart disease and stroke.

4. **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**: These increase the blood concentration of the incretin GLP-1 (glucagon-like peptide 1) by inhibiting its degradation by DPP-4, for example, sitagliptin (Januvia). However, sitagliptin and other DPP-4 inhibitors may also influence the tissue levels of other hormones and peptides.

5. **GLP-1 Agonists**: There is one approved drug, exanatide, a 39 amino acid polypeptide that acts as an agonist to the incretin GLP-1, which stimulates insulin secretion in the presence of high glucose but must be injected due to a lack of oral bioavailability.

6. **α-Glucosidase Inhibitors**: These are rarely used in the United States because of the severity of their side effects (flatulence and bloating); they do not have a direct effect on insulin secretion or sensitivity but act by slowing the digestion of starch in the small intestine. They may only be helpful in combination with other medications.

7. **SGLT2 Inhibitors**: Sodium glucose transporter 2 (SGLT2) accounts for 90% of the glucose reabsorption in the kidney. SGLT2 inhibitors increase urinary excretion of glucose and lower plasma glucose levels in an insulin-independent manner. Examples are the experimental drugs dapagliflozin and canagliflozin.

In spite of the large number of available medications, there is still an unmet medical need for orally effective new treatments for diabetes that will effectively regulate glucose homeostasis with better safety profiles and reduced adverse effects. The inventions in the three patent applications highlighted below address this unmet need. They relate to compounds that possess the abilities to modulate the G-protein-coupled receptor GPR119, which has been identified in recent years as a promising target for the treatment of diabetes mellitus, obesity, and other metabolic disorders. GPR119 is expressed predominantly in the β-cells of the pancreas and in the K- and L-cells of the intestine. Recent results from in vitro systems and animal model studies show that modulation of GPR119 may produce favorable effects on glucose homeostasis (without the risk of hypoglycemia), food intake, body weight gain, and possibly also β-cell preservation.

The stimulation of GPR119 increases the intracellular accumulation of the cyclic adenosine monophosphate (cAMP), leading to enhanced glucose-dependent insulin secretion from pancreatic β-cells and increased release of the incretin hormones GLP-1, GIP (glucose-dependent insulinotropic peptide), and PYY (polypeptide YY). The activation of GPR119 can be achieved by endogenous stimulants such as oleoylethanolamide and by small molecule agonists such as those described in the highlighted patent applications. Oral administration of small molecule GPR119 agonists has been shown to improve glucose tolerance in both rodents and humans.

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Table continued

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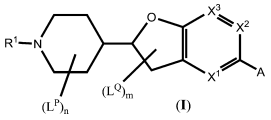
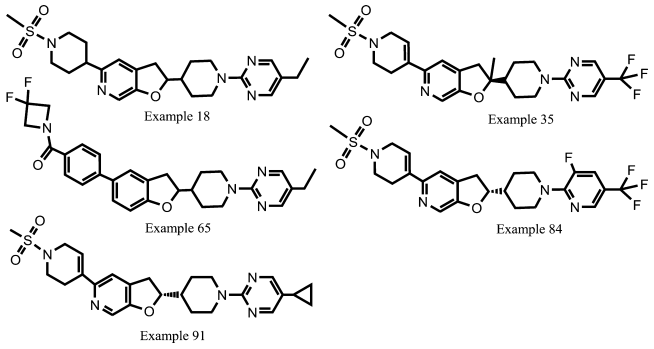
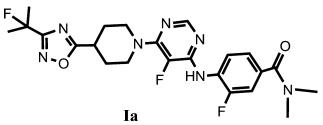
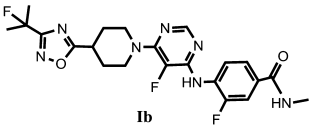
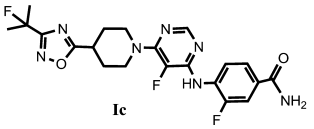
	The increase of the levels of the incretins GLP-1, GIP, and PYY as a result of GPR119 stimulation may additionally provide potential treatments to other disorders and diseases. GLP-1 receptor agonists are additionally useful in protecting against myocardial infarction and cognitive and neurodegenerative disorders. GIP has been shown to activate osteoblastic receptors, resulting in increases in collagen type I synthesis and alkaline phosphatase activity, both associated with bone formation. PYY is associated with reduced food intake and body weight gain in rodent models. PYY, which acts as an agonist for Y2R, can confer protection against inflammatory bowel disease and Crohn's disease. There are also reports that agonists of Y2R such as PYY can suppress tumor growth in pancreatic cancer (More detailed information can be found in the "background of the invention" included in all applications, particularly the details and references cited in WO 2012/040279).
Recent Review Articles:	1. Hansen, H. S.; Rosenkilde, M. M.; Holst, J. J.; Schwartz, T. W. *Trends Pharmacol. Sci.* **2012**, *33* (7), 374−381. 2. Shenoy, P. A.; Bandawane, D. D.; Chaudhari, P. D. *Int. J. Pharm. Sci. Res.* **2011**, *2* (10), 2490−2500. 3. Carpino, P. A.; Goodwin, B. *Expert Opin. Ther. Pat.* **2010**, *20* (12), 1627−1651. 4. Overton, H. A.; Fyfe, M. C. T.; Reynet, C. *Br. J. Pharmacol.* **2008**, *153* (Suppl. 1), S76−S81.
Patent Highlight 1	
Title:	Fused Dihydrofurans as GPR119 Modulators for the Treatment of Diabetes, Obesity, and Related Disorders
Patent Application Number:	WO 2012/098217 A1 **Publication Date:** July 26, 2012
Priority Application:	EP 11151688.6 **Priority Date:** January 21, 2011 EP 11191903.1 December 5, 2011
Inventors:	Himmelsbach, F.; Langkopf, E.; Nosse, B.
Assignee Company:	Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE)
Disease Area:	Diabetes, obesity, and related disorders **Biological Target:** G-protein-coupled receptor GPR119
Summary:	The invention in this patent application relates to novel compounds of formula (I) and their use as modulators of the G-protein-coupled receptor GPR119. These GPR119 agonists can potentially provide a treatment for types 1 and 2 diabetes, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, metabolic syndrome, obesity, high blood pressure, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, endothelial dysfunction, and bone-related diseases (such as osteoporosis, rheumatoid arthritis, or osteoarthritis).
Important Compound Classes:	 (I)
Key Structures:	 Example 18 Example 35 Example 65 Example 84 Example 91
Biological Assay:	The effect of the compounds on the activation of GPR119 and on the stimulation of intracellular cAMP concentration is determined using the AlphaScreen cAMP Assay Kit (Catalog #6760625R) made by PerkinElmer.
Biological Data:	Author: The EC_{50} values in nanomolar were reported for all 94 examples from the lowest (2 nM), for example, **18** and **84**, to the highest (228 nM), for example, **65**. The following table contains the EC_{50} values for the structures illustrated above.

Compound	EC_{50} (nM)	Compound	EC_{50} (nM)
Example 18	2	Example 35	3
Example 65	228	Example 84	2
Example 91	3		

Claims:	Claim 1: composition of matter, compounds of formula I with definitions of groups and substituents Claims 2−8: variations and more specific definitions for the groups in formula I Claims 9 and 10: pharmaceutical compositions Claim 11: method for treating disease or conditions mediated by activation of GPR119 Claim 12: method of treating diabetes, obesity, or dyslipidemia

Table continued

Patent Highlight 2			
Title:	Modulators of the GPR119 Receptor and the Treatment of Disorders Related Thereto		
Patent Application Number:	WO 2012/040279 Al	**Publication Date:**	March 29, 2012
Priority Application:	US 61/385,410 US 61/478,262	**Priority Date:**	September 22, 2010 April 22, 2011
Inventors:	Jones, R. M.; Lehmann, J.; Chen, W.; Edwards, J.; Marquez, G.; Morgan, M. E.; Sadeque, A. J. M.		
Assignee Company:	Arena Pharmaceuticals, Inc., San Diego, California, United States		
Disease Area:	Diabetes and obesity and related disorders	**Biological Target:**	G-protein-coupled receptor GPR119
Summary:	The invention in this patent application relates to the three compounds **Ia**, **Ib**, and **Ic**, which bind to and modulate the activity of the G-protein-coupled receptor GPR119. These compounds can potentially treat diabetes, obesity, and related metabolic diseases. For the treatment of T2D, each of these compounds may be used alone or in combination with a second pharmaceutical agent selected from a DPP-4 inhibitor, a biguanide, an α-glucosidase inhibitor, an insulin analogue, a sulfonylurea, an SGLT2 inhibitor, a meglitinide, a thiazolidinedione, and an antidiabetic peptide analogue.		
Important Compound Classes:	This patent application lists no general formula and claims only three compounds **Ia**, **Ib**, and **Ic**. All three have similar structures except for the terminal amide functionality, as seen in the key structures below.		
Key Structures:	 **Ia**  **Ib**  **Ic**		
Selected Biological Data:	1. Homogeneous time-resolved fluorescence (HTRF) assay for direct cAMP measurement		

Compound	EC_{50} (nM)	Compound	EC_{50} (nM)	Compound	EC_{50} (nM)
Ia	23.4	Ib	27.0	Ic	28.2

2. In vivo metabolism of compound **Ia**

The in vivo metabolism of compound **Ia** in mouse, rat, dog, and monkey produced compounds **Ib** and **Ic** among three main metabolites. The third metabolite was the corresponding carboxylic acid. The carboxylic acid shows very little activity in the HTRF assay (EC_{50}, 100 mM).

Claims:	There are 57 claims. Claims 1−3 are composition of matter; the remaining claims are for detailed methods for the use of any of the three compounds as medicament alone or in combination with other agents to treat patients with disease or disorder that may benefit from the GPR119 agonist activity.

Patent Highlight 3			
Title:	4-(5-Cyanopyrazol-1-yl)piperidine Derivatives as GPR119 Modulators		
Patent Application Number:	WO 2012/069948 Al	**Publication Date:**	May 31, 2012
Priority Application:	US 61/416,441	**Priority Date:**	November 23, 2010
Inventors:	Mascitti, V.; Mcclure, K. F.; Munchhof, M. J.; Robinson, R. P., Jr.		
Assignee Company:	Pfizer, Inc., 235 East 42nd Street, New York, New York 10017, United States		
Disease Area:	Diabetes	**Biological Target:**	G-protein-coupled receptor GPR119
Summary:	The invention in this patent application relates to a group of cyanopyrazole derivatives that modulate the activity of the G-protein-coupled receptor, GPR119. The patent application mentioned a long list of diseases and disorders that may benefit from these GPR119 agonists. The following is an abbreviated list of potential diseases and disorders mentioned: hyperlipidemia, types 1 and 2 diabetes mellitus, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, myocardial infarction, dyslipidemia, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, macular degeneration, cataract, diabetic nephropathy, chronic renal failure, diabetic neuropathy, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, neurological disorders such as Alzheimer's disease, schizophrenia, gastrointestinal illnesses such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome.		
Important Compound Classes:	The patent application does not describe a general formula; it lists and claims 80 compounds specifically by chemical name. Five of the 80 compounds were reclaimed separately; their structures are shown below as key structures.		

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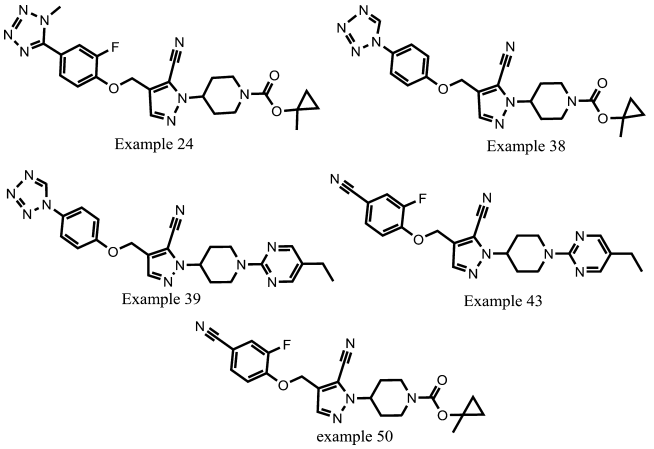
Table continued

Patent Highlight 3

Key Structures:



Biological Data:

The patent application provides a table with test results from the β-lactamase, β-arrestin, cAMP, and binding assays for 68 examples. The following data were reported for the five examples (24. 38, 39, 43, and 50) shown above:

Example Number	Human β-lactamase functional EC_{50} (nM)	Intrinsic activity (%)*	Human cAMP Functional EC_{50} (nM)	Intrinsic activity (%)	Human β-arrestin functional EC_{50} (nM)*	Intrinsic activity (%)	Human Binding Ki (nM)*
24	141	103	43.6	124	62.9	107	99
38			22.1	122	15	99.8	29.8
39			10.7	76.8	5.32	86.1	14.9
43			2.78	75.5	5.36	82.5	9.25
50			19.3	120	30.2	97.6	36.5

*The intrinsic activity is the percent of maximal activity of the test compound, relative to the activity of a standard GPR119 agonist.

Claims:

Claim 1: a list of 80 specific compounds by chemical name

Claim 2: reclaim of five of the above compounds (examples 24, 38, 39, 43, and 50 above)

Claims 3–12: pharmaceutical compositions, use as medicaments, etc. Claim 9 specifies a long list of possible diseases and disorders that can potentially be treated.

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Notes

The authors declare no competing financial interest.