ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Pyrimidinylpiperdinyloxypyridone Analogues as GPR119 Modulators

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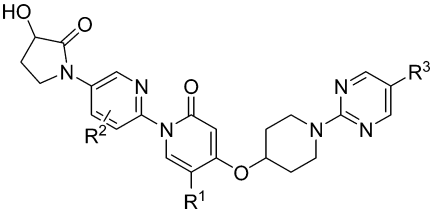
Title:	Pyrimidinylpiperdinyloxypyridone analogues as GPR119 modulators		
Patent/Patent Application Number:	WO2013173198	**Publication date:**	November 21st, 2013
Priority Application:	US61647772	**Priority date:**	May 16th, 2012
Inventors:	Broekema, Matthias; Wu, Gang; Wacker, Dean A.		
Assignee Company:	Bristol-Myers Squibb Company		
Disease Area:	Diabetes	**Biological Target:**	G protein-coupled receptor 119 (GPR119)

Summary: It is estimated that the global occurrence of diabetes mellitus exceeds 100 million patients. In the United States, an estimated 12 million people live with this condition, and the number of patients is expected to rise as the population ages. Characterized by abnormal glucose homeostasis resulting in elevated blood sugar levels, the root cause of this disease can be traced to either insufficient insulin secretion or ineffective use of insulin for the purposes of glucose regulation. The accumulation of blood glucose leads to hyperglycemia, which in time leads to a range of serious health issues. GPR119 has been identified as a potential target for the treatment of diabetes. It has been demonstrated that activation of this GPCR, which is present in pancreatic b-cells of a number of species, triggers a glucose-dependent increase in insulin secretion. The application of GPR119 agonists also induces improved performance in mouse glucose tolerance tests, a model commonly used for the assessment of antidiabetic agents. Reduced plasma glucose concentrations, decreased food intake, and reduced body weight have also been reported with chronic administration of GPR119 agonists, further supporting therapeutic potential for GPR119 agonists. The present application describes a series of pyridine analogues capable of modulating GPR119 activity and compositions useful for the treatment of diseases associated with GPR119 activity, such as diabetes and obesity.

Important Compound Classes:



Definitions:

R^1 is hydrogen or halo;
R^2 is (C_1-C_{10}) alkyl; and
R^3 is halo or (C_1-C_{10}) alkyl.

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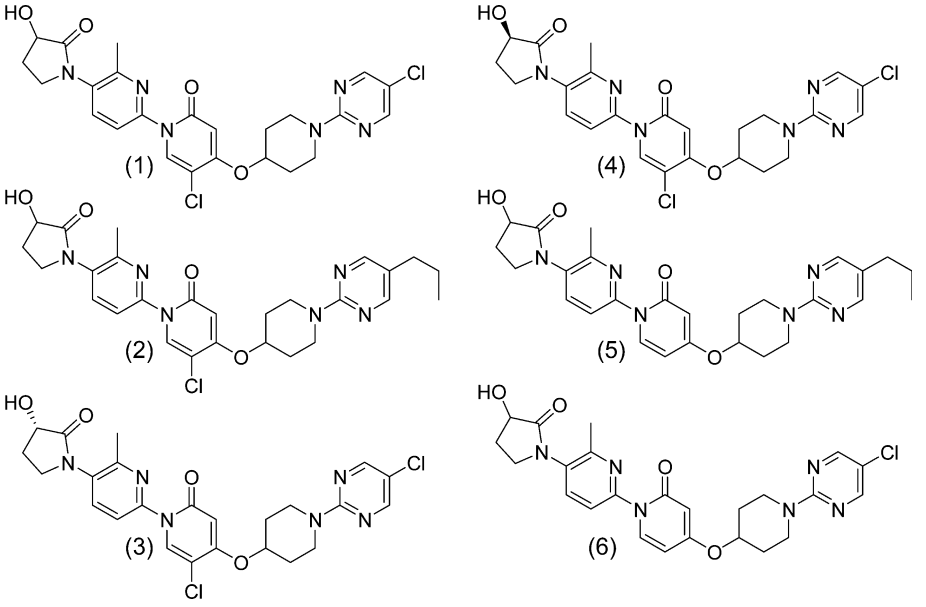
Key Structures:



Recent Review Articles

Shah, U. GPR119 agonists: a promising new approach for the treatment of type 2 diabetes and related metabolic disorders. *Curr. Opin. Drug Discovery Dev.* **2009**, *12* (4), 519−532.

Shah, U.; Edmondson, S.; Szewczyk, J. W. Recent advances in the discovery of GPR119 agonists. *RSC Drug Discovery Ser.* **2012**, *27*, 177−214.

Jones, R. M.; Leonard, J. N. The emergence of GPR119 agonists as anti-diabetic agents. *Annu. Rep. Med. Chem.* **2009**, *44*, 149−170.

Biological Assays:

Tet-inducible cAMP assay

Mouse oral glucose tolerance test

Human liver microsomal (HLM) stability

Biological Data:

Example	GPR119 EC_{50} (nM)	Glucose lowering (%, dose)	HLM $T_{1/2}$ (Min)
1	2	-36%, 0.03 mg/kg	94
2	4	-19%, 0.03 mg/kg	120
3	4	-26%, 0.03 mg/kg	78
4	3	-39%, 0.03 mg/kg	97
5	16	-21%, 0.1 mg/kg	76
6	10	Not Reported	101

Claims:

15 Total claims.

13 Composition of matter claims.

2 Method of use claims.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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