ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Prostaglandin EP3 Receptor Antagonists May Provide Novel Treatment for Diabetes

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Title:	Antagonists of Prostaglandin EP3 Receptor		
Patent Application Number:	WO 2015/052610 A1	**Publication date:**	16 April 2015
Priority Application:	US 61/888,822	**Priority date:**	9 October 2013
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Assignee Company:	Pfizer Inc.; 235 East 42nd Street, New York, New York 10017, USA		
Disease Area:	Type II diabetes	**Biological Target:**	Prostaglandin EP3 receptor

Summary:

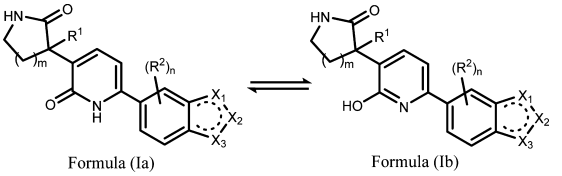
The invention in this patent application relates to heterocyclic compounds represented generally by formula (I). The compounds of formula (I) may be represented by either one of two possible keto−enol tautomeric forms, 2-pyridinone derivatives (Ia) or 2-hydroxypyridine derivatives (Ib). These compounds are EP3 receptor antagonist that may be used for the treatment of Type II diabetes. They may also be useful for the treatment of any one of the following disorders: bladder overactivity, cerebrovascular disease, coronary artery disease, hypertension, neurodegenerative disorders, pain, premature labor, restenosis, and thrombosis.

Type I diabetes represents about 5−10% of all diabetes cases and occurs as a result of destruction of the pancreatic beta cells, which produce the hormone insulin, by the body's own immune system. The patients are completely dependent on insulin treatment for survival. Type II diabetes is more common (90−95% of all cases). It starts as insulin resistance particularly in the cells of liver, muscle, and adipose tissue that become resistant to the effects of insulin in stimulating glucose and lipid metabolism. As the disease progresses the pancreas gradually loses its ability to produce insulin and if not properly controlled with medication it may lead to pancreatic beta-cell failure requiring complete dependence on insulin. While there are five different categories of Type II diabetes medications, they may be ineffective and/or cause undesirable adverse effects such as hypoglycemia, gastrointestinal disturbances, lactic acidosis, weight gain, edema, and anemia. There continues to be a need to introduce new effective treatments that may be used less frequently, preferably causing fewer side effects and can act either by increasing the endogenous insulin secretion or independently from the actions of insulin.

Studies have provided strong evidence that underscores the role of increased levels of prostaglandin E2 (PGE2) as a contributor to defective insulin secretion in diabetic patients. It has been determined that PGE2 inhibits glucose-stimulated insulin secretion (GSIS) in humans. However, it was also established that the inhibition of PGE2 production can partially restore acute GSIS. Other studies have confirmed that increased level of intracellular cyclic adenosine monophosphate (cAMP) is a critical component of the inhibitory action of PGE2 on GSIS.

There are four known PGE2 ligand receptors known as EP1, EP2, EP3, and EP4. The receptor EP3 has the strongest rationale as the prostanoid receptor that mediates the inhibitory effect of PGE2 on GSIS. Animal model studies have recently confirmed a functional link from PGE2 suppression of GSIS through EP3. These findings indicate that EP3 receptor antagonists, such as the compounds described in this patent application, may provide useful treatment for Type II diabetes by relieving the inhibitory action of PGE2 to partially restore defective GSIS in diabetic patients.

Important Compound Classes:

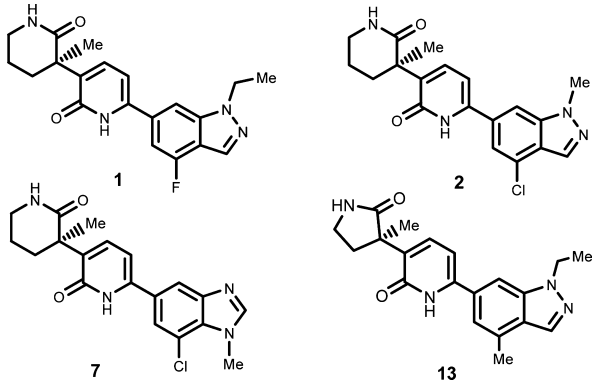


Formula (Ia) Formula (Ib)

Formula (I)

Received: May 6, 2015
Published: May 13, 2015

Key Structures: The inventors described the structures of 14 examples of formula (I) including the following four representative examples. All structures are presented as the 2-pyridinone tautomeric forms [formula (Ia)].



Biological Assay:

- EP3 Radioligand SPA Binding Assay

Biological Data: K_i values for the binding affinity against human EP3 are listed as geometric mean K_i values for the representative examples **1**, **2**, **7**, and **13**.

binding affinity against human EP3		
Compound	**Human EP3 Ki [nM]**	**n**
1	2.0	17
2	3.6	4
7	7.8	10
13	31.6	5

Recent Review Articles:

1. Kimple, M. E.; Keller, M. P.; Rabaglia, M. R.; Pasker, R. L.; Neuman, J. C.; Truchan, N. A.; Brar, H. K.; Attie, A. D. *Diabetes* **2013**, *62* (6), 1904−1912.
2. Neuman, J. C.; Kimple, M. E. *J. Endocrinol. Diabetes Obes.* **2013**, *1* (1), 1002−1004.

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Notes

The authors declare no competing financial interest.