ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Modulators of GPR40 as Treatment for Diabetes

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Title:	Dihydropyrazole GPR40 Modulators		
Patent Application Number:	WO 2014/078608 Al	**Publication Date:**	22 May 2014
Priority Application:	US 61/727,191	**Priority Date:**	16 November 2012
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Assignee Company:	Bristol-Myers Squibb Company, P.O. Box 4000, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, USA		
Disease Area:	Diabetes and related conditions	**Biological Target:**	GPR40 G protein-coupled receptor

Summary:

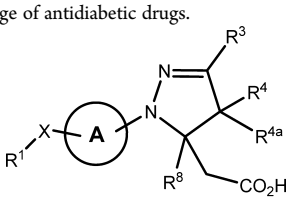
The invention in this patent application relates to novel carboxy dihydropyrazole derivatives represented generally by formula (I). These compounds are modulators of GPR40 (a G-protein coupled receptor) and may potentially be useful for the treatment or prophylaxis of diabetes and related conditions.

The type 2 diabetes is the most common form of diabetes mellitus. It is characterized by increasing insulin resistance associated with inadequate insulin secretion after a period of compensatory hyperinsulinemia. β-cells are located in the islets of Langerhans of the pancreas and primarily function to store and release insulin. Plasma free fatty acids (FFAs) are implicated in mediation of insulin resistance. They are believed to influence insulin secretion from β-cells mainly by enhancing glucose-stimulated insulin secretion (GSIS).

The G-protein coupled receptors (GPCRs) expressed in the β-cells are known to modulate the release of insulin in response to changes in plasma glucose levels. One of the G-protein coupled receptors is GPR40, also known as fatty acid receptor 1 (FFAR1). It is a membrane-bound FFA receptor, which is expressed in the pancreatic islets, specifically in β-cells, and mediates medium to long chain fatty acid induced insulin secretion. GPR40 is also expressed in enteroendocrine cells wherein activation promotes the secretion of gut incretin hormones, such as GLP-1, GIP, CCK, and PYY. These hormones stimulate insulin secretion in response to meals.

GPR40 modulators such as the compounds described in this patent application may potentially provide a treatment for type 2 diabetes and enhanced glycemic control through exerting an incretin effect to promote GSIS. It may also be potentially effective when used in combination with a broad range of antidiabetic drugs.

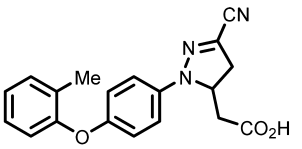
Important Compound Classes:



Formula (I)

Received: July 2, 2014
Published: July 09, 2014

Key Structures: The inventors described the synthesis of 78 examples of formula (I) compounds. Many of the compounds were resolved into pure enantiomers. The following compounds are representative of the disclosed compounds in which both enantiomers were isolated and labeled as isomers 1 and 2:



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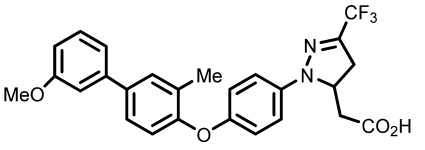

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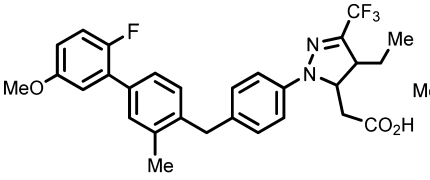

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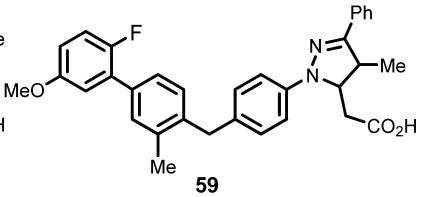

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Biological Assay: *In Vitro* GPR40 Assays:

- FDSS-Based Intracellular Calcium Assay
- GPR40 IP-One HTRF Assays in HEK293/GPR40 Inducible Cell Lines

In Vivo GPR40 Assays

- Acute Oral Glucose Tolerance Test
- Acute Oral Glucose Tolerance Test in Rats

Biological Data: The disclosed examples were tested in the human GRP40 *in vitro* assay and found having hGRP40 modulating activity reported as hGPR40 EC_{50}. The following Table contains the EC_{50} data for the above examples:

Example	hGPR40 EC_{50} (nM)	
	Isomer 1	Isomer 2
3	37	560
9	190	290
44	1310	20
59	6470	6

Claims: Claims 1−10: Composition of matter, variations of formula (I)

Claims 11−13: Pharmaceutical composition

Claims 14−15: Use of compounds

Recent Review Articles:

Poitout, V.; Lin, D. C.-H. *Drug Discovery Today* **2013**, *18*(23−24), 1301−1308.

Basu, A.; Kudva, Y. C.; Basu, R. *Diabetes Care* **2013**, *36*(2), 185−187.

Vangaveti, V.; Shashidhar, V.; Jarrod, G.; Baune, B. T.; Kennedy, R. L. *Ther. Adv. Endocrinol. Metab.* **2010**, *1*(4), 165−175.

Medina, J. C.; Houze, J. B. *Annu. Rep. Med. Chem.* **2008**, *43*, 75−85.

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Notes

The authors declare no competing financial interest.