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PATENT HIGHLIGHT

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Prokineticin Receptor Modulators May Potentially Treat Psychiatric and Neurological Disorders

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Patent Application Title:	Piperidine Derivatives for Use in the Treatment or Prevention of Psychiatric and Neurological Conditions		
Patent Application Number:	WO 2015/079224 Al	**Publication date:**	4 June 2015
Priority Application:	GB 1320905.1	**Priority date:**	27 November 2013
Inventors:	Goldby, A.; Jenkins, K.; Teall, M.		
Assignee Company:	Takeda Cambridge Limited; 418 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 OPA, U.K. (for MG only) Takeda Pharmaceutical Company Limited; 1-1, Doshomachi 4-Chome, Chou-Ku, Osaka-Shi, Osaka 541-0045, Japan		
Disease Area:	Treatment or prevention of psychiatric and neurological conditions	**Biological Target:**	Prokineticin receptor 1 (PKR1)

Summary:

The invention in this patent application relates to piperidine derivatives represented generally by formula (I) that are prokineticin receptor (PKR) modulators and may provide treatment or prevention for psychiatric and neurological conditions.

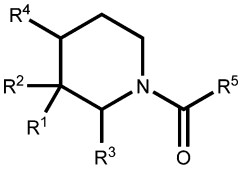
Prokineticin proteins (PK1 and PK2) contain 86 and 81 amino acids, respectively, and share 45% amino acid identity. Initially, they were identified as potent mediators of gut motility. However, they were later shown to promote other functions including angiogenesis in steroidogenic glands (e.g., adrenal gland), heart, and reproductive systems. They also modulate neurogenesis, circadian rhythms, nociceptin, hematopoiesis, and the immune response. In addition, they are associated with pathologies of the reproductive and nervous systems, myocardial infarction, and tumorigenesis. There are two prokineticin receptors, prokineticin receptor 1 (PKR1) and prokineticin receptor 2 (PKR2); the two receptors show 87% homology.

Prokineticin receptor 1 (PKR1) couples to Gq/Gu proteins; this activity leads to the activation of phospholipase C, production of inositol phosphate, calcium mobilization, and activation of the mitogen-activated protein kinase (MAPK) pathways. PKR1 is broadly distributed throughout peripheral tissues including the intestinal tract, testis, uterus, lung, macrophage, bone, heart, rectum, white adipose and peripheral blood leukocytes. It is also expressed in the brain particularly in the olfactory regions as well as in dorsal root ganglion (DRG) neurons, hippocampus, dentate gyrus, cerebellar cortex, cerebral cortex, amygdala, medulla oblongata, and spinal cord.

Therefore, the antagonism of the functions of the prokineticin receptors may potentially provide a useful therapeutic tool for the treatment of several disorders or diseases including gastrointestinal motility, angiogenesis, hematopoiesis, diabetes, and pain.

The compounds described in this patent application are prokineticin receptor modulators that act by blocking PKR1 activities. They display favorable potency, selectivity, and/or pharmacokinetic properties. These compounds may provide treatment and/or prophylaxis for multiple disorders whose development or symptoms are linked to prokineticin receptor activities. The inventors mentioned many disorders that may potentially be benefited from treatment with prokineticin receptor modulators including but not limited to the positive symptoms of schizophrenia, schizophreniform disorder, or schizoaffective disorder, cognitive disorders (such as dementia and impaired learning), pain (such as neuropathic pain), irritable bowel diseases, and irritable bowel syndrome.

Important Compound Classes:



Formula (I)

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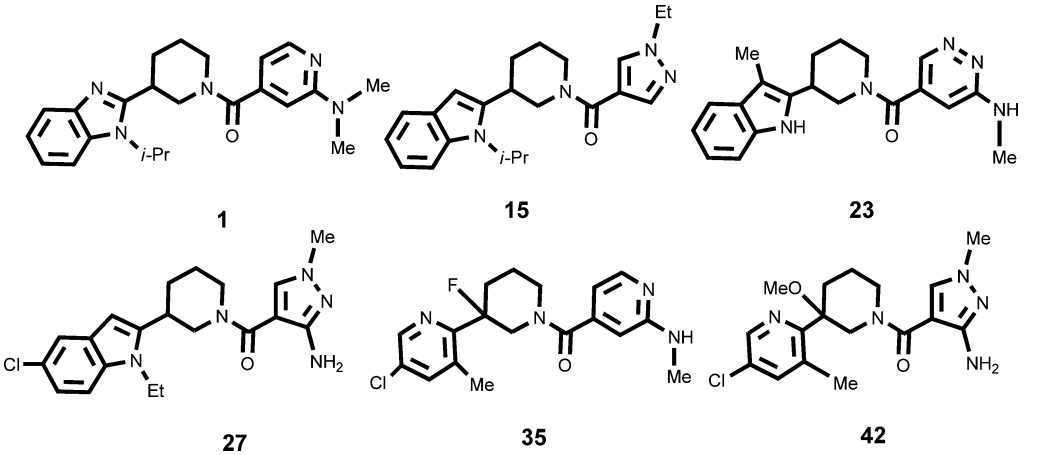
Key Structures: The inventors described the structures and syntheses of 43 compounds of formula (I) including the following representative examples:



Biological Assay: The PKR1 antagonist activities of the invention's compounds were determined by their abilities to block the intracellular release of calcium mediated by PK1 in RBL2H3 cells expressing human PKR1 receptors.

Biological Data: The mean IC_{50} values were determined from a minimum of two independent assays for each compound. The assay data obtained from the above representative examples are listed in the following table:

Compound	Mean IC_{50} (μM)
1	0.32
15	0.33
23	7.41
27	0.91
35	0.29
42	>9

Recent Review Articles:

1. Nguyen, T. L.; Gasser, A.; Nebigil, C. G. *J. Dev. Biol.* **2013**, *1* (1), 20−31.
2. Abreu, A. P.; Kaiser, U. B.; Latronico, A. C. *Neuroendocrinology* **2010**, *91*(4), 283−290.
3. Ngan, E. S. W.; Tam, P. K. H. *Int. J. Biochem. Cell Biol.* **2008**, *40*(9), 1679−1684.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.