Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to initiate signal transduction leading to a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by a ligand or a compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

SUMMARY ~~OF THE INVENTION~~

The present invention relates to the unexpected discovery by Applicant that administration of a GPR119 agonist to an individiual, such as by oral administration, can act at GPR119 receptor to increase a GIP level in the individual. The present invention features methods relating to GPR119 for identifying GIP secretagogues, compounds useful for treating or preventing a condition characterized by low bone mass, such as osteoporosis, and compounds useful for increasing bone mass in an individual. A GPR119 agonist is useful for promoting (e.g., increasing) bone formation in an individual. In certain embodiments, the individual is a human.

Nucleotide sequence encoding human GPR119 polypeptide is given in SEQ ID NO: 1. The amino acid sequence of said encoded human GPR119 polypeptide is given in SEQ ID NO: 2.

In a ***first aspect***, the invention features a method for identifying GIP secretagogues, compounds useful for treating or preventing a condition characterized by low bone mass, or compounds useful for increasing bone mass in an individual, comprising the steps of:

(a) contacting a test compound with a host cell or with membrane of a host cell comprising a G protein-coupled receptor, wherein the G protein-coupled receptor comprises an amino acid sequence selected from the group consisting of:

(i) amino acids 1-335 of SEQ ID NO:2;

(ii) amino acids 2-335 of SEQ ID NO:2;

(iii) amino acids 2-335 of SEQ ID NO:2, with the proviso that the G protein-coupled receptor does not comprise the amino acid sequence of SEQ ID NO:2;

(iv) the amino acid sequence of a G protein-coupled receptor encoded by a polynucleotide that is amplifiable by polymerase chain reaction (PCR) on a human DNA sample using specific primers SEQ ID NO:3 and SEQ ID NO:4;

International Application No. PCT/GB2006/050177 (published as WO 2007/003961); International Application No. PCT/GB2006/050178 (published as WO 2007/003962); International Application No. PCT/GB2006/050182 (published as WO 2007/003964); or International Application No. PCT/JP02/09350 (published as WO 03/026661). In certain embodiments, the known ligand is (2-Fluoro-4-methanesulfonyl-phenyl)-{6-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-5-nitro-pyrimidin-4-yl}-amine. In certain embodiments, the known ligand is an endogenous ligand of an endogenous vertebrate, mammalian, or human GPR119 receptor.

In certain embodiments, the optionally labeled known ligand is a labeled known ligand. In certain embodiments, the labeled known ligand is a radiolabeled known ligand. Techniques for radiolabeling a compound, such as for labeling a known ligand of a G protein-coupled receptor of the invention, are well known to the skilled artisan. *See*, e.g., International Application WO 04/065380. Also see, e.g., Example 11, *infra*.

Techniques for detecting the complex between a G protein-coupled receptor and a compound known to be a ligand of the G protein-coupled receptor are well known to the skilled artisan. *See*, e.g., International Application WO 04/065380. Also see, e.g., Example 12, *infra*.

In some embodiments, the method further comprises the step of optionally determining the structure of the GIP secretagogue, the compound useful for treating or preventing a condition characterized by low bone mass, or the compound useful for increasing bone mass in an individual.

In some embodiments, the method further comprises the step of optionally providing the name or structure of the GIP secretagogue, the compound useful for treating or preventing a condition characterized by low bone mass, or the compound useful for increasing bone mass in an individual.

In some embodiments, said method further comprises the step of optionally producing or synthesizing the GIP secretagogue, the compound useful for treating or preventing a condition characterized by low bone mass, or the compound useful for increasing bone mass in an individual.

In some embodiments, said method further comprises the step of formulating the GIP secretagogue, the compound useful for treating or preventing a condition characterized by low bone mass, or the compound useful for increasing bone mass in an individual as a pharmaceutical.

In some embodiments, said method further comprises the step of formulating the GIP secretagogue, the compound useful for treating or preventing a condition characterized by low bone mass, or the compound useful for increasing bone mass in an individual into a pharmaceutical composition.

In one aspect, there is provided a method of preparing a pharmaceutical composition comprising a G protein-coupled receptor 119 (GPR119) agonist having the effect of a glucose-dependent insulinotropic peptide (GIP) secretagogue, the method comprising:

(a) contacting, in vitro, the GPR119 agonist with a vertebrate enteroendocrine cell or with a cell capable of secreting GIP,

(b) determining whether the GPR119 agonist stimulates GIP secretion from the vertebrate enteroendocrine cell or from the cell capable of secreting GIP; wherein the ability of the GPR119 agonist to stimulate GIP secretion from the vertebrate enteroendocrine cell or from the cell capable of secreting GIP is indicative of the agonist being a GIP secretagogue; and

(c) formulating the GPR119 agonist having the effect of a GIP secretagogue with a pharmaceutically acceptable carrier.

In one aspect, there is provided a method of preparing a pharmaceutical composition comprising a GPR119 agonist having the effect of a GIP secretagogue, the GPR119 agonist having been contacted *in vitro* with a vertebrate enteroendocrine cell or with a cell capable of secreting GIP and determined to stimulate GIP secretion from the vertebrate enteroendocrine cell or from the cell capable of secreting GIP, wherein the ability of the GPR119 agonist to stimulate GIP secretion from the vertebrate enteroendocrine cell or from the cell capable of secreting GIP is indicative of the agonist being a GIP secretagogue, the method comprising formulating the GPR119 agonist having the effect of a GIP secretagogue with a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated in connection with the figures appended hereto in which:

FIG. 1 shows a pharmacodynamic analysis of an effect of administration of GPR119 agonist on blood GIP level in wild-type mice. **A.** A time course analysis carried out using **Compound 1** as