

SMALL MOLECULE MODULATORS OF G PROTEIN-COUPLED RECEPTOR SIX

RELATED CASES

This patent document is related to U.S. Patent Application 09/364,425 filed via Express Mail on July 30, 1999 claiming the benefit of commonly owned: (1) Provisional Patent Application Serial Number 60/094,879, filed July 31, 1998; (2) Provisional Patent Application Serial Number 60/106,300, filed October 30, 1998; (3) Provisional Patent Application Serial Number 60/110,906, filed December 4, 1998; (4) Provisional Patent Application Serial Number 60/121,851, filed February 26, 1999 (5) Provisional Patent Application Serial Number 60/173,850, filed December 30, 1999; and (6) Provisional Patent Application Serial Number 60/174,428, filed January 4, 2000. The disclosure of each of the foregoing patent documents is incorporated in its entirety herein by reference. Priority benefit of aforementioned U.S. Application Ser. No. 09/364,425 and Provisional Patent Applications (4), (5) and (6) above is hereby claimed.

FIELD OF INVENTION

The present invention relates to small molecule modulators of G protein-coupled receptor six (GPR6); preferably, the small molecule modulators are preferentially selected for the human GPR6; most preferably, the small molecule modulators are inverse agonists to the human GPR6.

BACKGROUND OF THE INVENTION.

A. G Protein-Coupled Receptors

G protein-coupled receptors (GPCR) share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi, and Go are G proteins that have been identified.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries, including but not exclusively limited to, modifications to the amino acid sequence of the receptor, provide alternative mechanisms other than ligands to stabilize the active state conformation. These approaches effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent approaches is termed "constitutive

receptor activation." A receptor for which the endogenous ligand is unknown or not identified is referred to as an "orphan receptor."

B. Traditional Compound Screening

Generally, the use of an orphan receptor for screening purposes to identify compounds that modulate a biological response associated with such receptor has not been possible. This is because the traditional "dogma" regarding screening of compounds mandates that the ligand for the receptor be known, whereby compounds that competitively bind with the receptor, *i.e.*, by interfering or blocking the binding of the natural ligand with the receptor, are selected. By definition, then, this approach has no applicability with respect to orphan receptors. Thus, by adhering to this dogmatic approach to the discovery of therapeutics, the art, in essence, has taught and has been taught to forsake the use of orphan receptors unless and until the natural ligand for the receptor is discovered. The pursuit of an endogenous ligand for an orphan receptor can take several years and cost millions of dollars.

Furthermore, and given that there are an estimated 2,000 GPCRs in the human genome, the majority of which being orphan receptors, the traditional dogma castigates a creative approach to the discovery of therapeutics to these receptors.

Numerous orphan G protein-coupled receptors are constitutively active in their endogenous state. GPR6 is a 362 amino acid homolog of GPR3; the endogenous ligand for GPR6 is unknown (Song, Z.-H. et al, *supra.*; see Figure 1 for reported amino acid sequence). GPR6 transcripts are reported to be abundant in the human putamen and to a lesser extent in the frontal cortex, hippocampus, and hypothalamus (Heiber, M. et al. *DNA and Cell Biology* (1995) 14(1): 25; see Figure 1 for reported nucleic acid and amino acid sequences for GPR6).

C. Obesity

Recently, our current knowledge of human obesity has advanced dramatically. Previously, obesity was viewed as an oppugnant behavior of inappropriate eating in the setting of appealing foods. Studies of animal models of obesity, biochemical alterations in both humans and animals, and the complex interactions of psychosocial and cultural factors that create receptiveness to human obesity indicate that this disease in humans is multifaceted and deeply entrenched in biologic systems. Thus, it is almost certain that obesity has multiple causes and that there are different types of obesity.

An increasing number of children and adolescents are overweight. Although not all overweight children will necessarily become overweight adults, the growing occurrence of obesity in childhood is likely to be reflected in increasing obesity in adult years. The high prevalence of obesity in our adult population and the likelihood that the nation of the future will be even more obese demands a re-examination of the health implications of this disease. See, Health Implications of Obesity. NIH Consens. Statement Online 1985 Feb 11-13; 5(9):1-7.

"Clinical obesity" is a measurement of the excess body fat relative to lean body mass and is defined as a body weight more than 20% above the ideal body weight. Recent estimates suggest that 1 in 2 adults in the United States is clinically obese, an increase of more than 25% over the past decades. Flegal MD., et al., 22 *Int. J. Obes. Relat. Metab. Disor.* 39 (1998). Both overweight conditions and clinical obesity are a major health concerns worldwide, in particular because clinical obesity is often accompanied by numerous complications, *i.e.*, hypertension and Type II diabetes, which in turn can cause coronary artery disease, stroke, late-stage complications of diabetes and premature death. (See, e.g., Nishina P.M. et al., 43 *Metab.* 554 (1994)).

Although the etiologic mechanisms underlying obesity require further clarification, the net effect of such mechanisms leads to an imbalance between energy intake and expenditure. Both genetic and environmental factors are likely to be involved in the pathogenesis of obesity. These include excess caloric intake, decreased physical activity, and metabolic and endocrine abnormalities.

Treatment of overweight conditions and clinical obesity via pharmaceutical agents are not only of importance with respect to the conditions themselves, but also with respect to the possibility of preventing other diseases that are associated with, *e.g.*, clinical obesity, as well as enhancement of the positive feeling of "self" that often accompanies those who are overweight or clinically obese and who encounter a significant reduction in body weight.

Given the foregoing discussion, it is apparent that compounds which help in the treatment of such disorders would be useful and would provide an advance in both research and clinical medicine. The present invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

The present invention relates to small molecule modulators of the GPR6 receptor. Most preferably, the GPR6 modulators have inverse agonist characteristics at the receptor.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphic representation of the results of a cell-based cyclic AMP assay providing comparative results for constitutive signaling GPR6 and GPR6:Fusion Protein.

Figure 2 is a graphic representation of the results of a [35 S]GTP γ S assay providing comparative results for constitutive signaling by GPR6 and GPR6:Fusion Protein.

Figure 3 is a graphic representation of results from a primary screen of several candidate compounds against GPR6; results for compound "ARE112" are provided in well H6.

Figure 4 is a graphic representation of an IC₅₀ curve for compound ARE112 against the GPR6 receptor, indicating an IC₅₀ value of 0.1501 μ M

Figures 5A, 5B and 5C provide graphic representations of the results of *in vivo* administration (IP) of ARE112 on cumulative food intake (5A), water intake (5B) and body weight gain (5C) on 24-hour food deprived rats.

Figures 6A, 6B and 6C provide graphic representations of the results of *in vivo* administration (IP) of ARE112 on cumulative food intake (6A), water intake (6B) and body weight gain (6C) on non food deprived rats.

Figure 7A, 7B and 7C provide graphic representations of the results of *in vivo* administration (ICV) of ARE112 on cumulative food intake (7A), water intake (7B) and body weight gain (7C) on 24-hour food deprived rats.

Figure 8 provides a graphic representation of the results of ARE112 on locomotor activity on rats 16 hours post-administration.

Figures 9A and 9B provide graphic representations of the results of *in vivo* administration (oral-gavage) of ARE112 on cumulative food intake on 24-hour food deprived rats (9A) and on cumulative food intake on non food deprived rats (9B).

Figures 10A, 10B and 10C provide graphic representations of the results of *in vivo* administration (oral-gavage) of structural analogs of ARE112 on cumulative food intake (10A), water intake (10B) and body weight gain (10C) on 24-hour food deprived rats.

Figure 11 provide a graphic representation of the results of a daily repeated *in vivo* (IP) administration of ARE112 rats showing a long-term decrease in body weight in non food deprived.

Figure 12 provide a graphic representation of the results of *in vivo* (oral-gavage) administration of ARE112 showing a decrease in startle reflex in non food deprived rats.

DEFINITIONS

The scientific literature that has evolved around receptors has adopted a number of terms. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control.

ACTIVE INGREDIENT in the context of a "Pharmaceutical Composition" shall mean a component of a Pharmaceutical Composition that provides the primary pharmaceutical benefit, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

AGONISTS shall mean moieties that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes. In the context of the disclosed invention, a Pharmaceutical Candidate comprising a GPR6 Agonist can be utilized for increasing body weight and/or affecting metabolism such that the recipient gains weight and/or maintains weight. Such can be used in the context of disorders and/or diseases where

weight loss is a component of the disease and/or disorder such as, for example, anorexia nervosa, cancer, AIDS cachexia, etc.

PARTIAL AGONISTS shall mean moieties that activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

ANTAGONIST shall mean moieties that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. **ANTAGONISTS** do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CANDIDATE COMPOUND, in the context of the disclosed invention, shall mean a small molecule that is amenable to a screening technique.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition comprising at least one Active Ingredient and at least one other component is a Composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity.

CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous ligand or a chemical equivalent thereof.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

ENDOGENOUS shall mean a material that a mammal naturally produces. **ENDOGENOUS** in reference to, for example and not limitation, the term "receptor" shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. In contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not a limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

G PROTEIN COUPLED RECEPTOR FUSION PROTEIN and **GPCR FUSION PROTEIN**, in the context of the invention disclosed herein, each mean a non-endogenous protein comprising an endogenous, constitutively activated orphan GPCR fused to at least one G protein, most preferably, the alpha (α) subunit of such G protein (this being the subunit that binds GTP), with the G protein preferably being of the same type as the G protein that naturally couples with endogenous orphan GPCR. For example, and not limitation, in an endogenous state, the G protein "G α " is the predominate G protein that couples with GPR6 such that a GPCR Fusion Protein based upon GPR6 would be a non-endogenous protein

comprising GPR6 fused to Gs α . The G protein can be fused directly to the c-terminus of the endogenous, constitutively active orphan GPCR or there may be spacers between the two.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean moieties that bind the endogenous form of the receptor, and which inhibit the baseline intracellular response initiated by the active endogenous form of the receptor below the normal base level of activity that is observed in the absence of the endogenous ligand, agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is decreased in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist. Biologically, "GPR6 inverse agonist" shall mean moieties that can be assessed *in vivo* by factors other than just determination that the moiety has interacted with GPR6, *e.g.*, when the moiety interacts with a mammal's GPR6 *in vivo*, there is an observed decrease in the mammal's body weight by at least about 5% within 24 to 48 hours of contacting GPR6 and the GPR6 inverse agonist.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at one Active Ingredient and at least one ingredient that is not an Active Ingredient (for example and not limitation, a filler, dye, or a mechanism for slow release), whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example,

and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

SMALL MOLECULE, in the context of the invention disclosed herein, is a non-protein based moiety; for example, and not limitation, ARB112 is a small molecule within the context of this invention, while the endogenous ligand for a receptor is not a small molecule.

DETAILED DESCRIPTION

A. Introduction

The traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been recognized is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases that result from an overly active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound (*e.g.*, therapeutic) that reduces the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state. The search, then, is for an inverse agonist to the active state receptor.

Screening candidate compounds against orphan receptors, for example, including and not limited to, GPR6 and GPR6 Fusion Protein, allows for the direct identification of candidate compounds which act at this orphan cell surface receptor, without requiring any prior knowledge or use of the receptor's endogenous ligand. By determining areas within the body where such receptors are expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression of these receptors; such an approach is disclosed in this patent document.

B. Disease/Disorder Identification and/or Selection

As will be set forth in greater detail below, most preferably inverse agonists and agonists to GPR6 can be identified by the methodologies of this invention. Such inverse agonists and agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to this receptor. Indeed, an antagonist to such a receptor (even if the ligand were known) may be ineffective given that the receptor is activated even in the absence of ligand-receptor binding. Because of the ability to directly identify inverse agonists and agonists to these receptors, thereby allowing for the development of pharmaceutical compositions, a search for diseases and disorders associated with these receptors is possible. For example, GPR6 is expressed in the following areas of the brain: lateral hypothalamus, hippocampus, nucleus accumbens, caudate and cerebral cortex. Given the high levels of expression in the areas of the brain associated with feeding behavior and metabolism, GPR6 is likely to be related to a variety of disorders and diseases related to abnormal food intake and/or metabolism, *e.g.*, clinical obesity.

C. Screening of Candidate Compounds

1. Generic GPCR screening assay techniques

When a G protein receptor becomes constitutively active, it binds to a G protein (for example Gq, Gs, Gi, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [³⁵S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that [³⁵S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. Generally, this preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (*i.e.* an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain. Thus, by screening those candidate compounds, which have been identified using a "generic" assay in an agonist and/or antagonist competitive binding assay, further refinement in the selection process is provided.

In the case of GPR6 it has been determined that this receptor couples the G protein Gs. Gs stimulates the enzyme adenylyl cyclase (Gi, on the other hand, inhibits this enzyme). Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, assays that detect cAMP can be utilized, for example and not limitation, cell-based cAMP assay, to determine if a candidate compound is an inverse agonist to the receptor (i.e., such a compound which contacts the receptor would decrease the levels of cAMP relative to the uncontacted receptor). As a result, "cyclase-based assays" can be used to further screen those compounds selected from an agonist and/or antagonist competitive binding assay.

3. GPCR Fusion Protein

The use of an endogenous, constitutively activated orphan GPCRs, such as GPR6, for use in screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists, provides a unique challenge in that, by definition, the endogenous receptor is active even in the absence of an endogenous ligand bound thereto. Thus, in order to differentiate between, *e.g.*, the endogenous receptor in the presence of a candidate compound and the endogenous receptor in the absence of that compound, with an aim of such a differentiation to allow for an understanding as to whether such compound may be an inverse agonist, agonist, partial agonist or have no affect on such a receptor, it is preferred that an approach be utilized that can enhance such differentiation. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that an endogenous orphan GPCR is constitutively activate, using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is

most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the endogenous, constitutively active orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that one will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the endogenous GPCR. The GPCR Fusion Protein appears to be important for screening with an endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques. This is important in facilitating a significant "signal to noise" ratio. A significant ratio is preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is that the endogenous GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the endogenous GPCR is upstream of the G protein sequence) and that the "stop" codon of the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12, although this number can be readily ascertained by one of ordinary skill in the art). Both

approaches have been evaluated, and in terms of measurement of the activity of the GPCR, the results are substantially the same; however, there is a preference (based upon convenience) for use of a spacer in that some restriction sites that are not used will, upon expression, effectively, become a spacer. Most preferably, the G protein that couples to the endogenous GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

D. Pharmaceutical Compositions

Candidate compounds selected for further development as active ingredients can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.).

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. The particular order of screening techniques set forth below is ranked for presentational efficiency. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make modifications to these sequences while achieving the same or substantially similar results reported below.

EXAMPLE 1

RECEPTOR EXPRESSION

1. cDNA and Vectors

The expression vector comprising GPR6 cDNA was generously supplied by Brian O'Dowd (University of Toronto). The vector utilized for GPR6 was pRcCMV (the coding region for GPR6 was subcloned into pCMV vector at a HindIII-XbaI site). See, SEQ.ID.NO.:1 for nucleic acid sequence and SEQ.ID.NO.:2 for the deduced amino acid sequence of GPR6.

2. Transfection Procedure

On day one, 1×10^7 293 cells per 150mm plate were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 20 μ g DNA (e.g., pCMV vector; pCMV vector GPR6 cDNA, pCMV vector GPR6:Fusion-Protein) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 120 μ l lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1X PBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture was then added to the cells, followed by incubation for 4hrs at 37°C/5% CO₂. The transfection mixture was then removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells were then incubated at 37°C/5% CO₂. After 72hr incubation, cells were then harvested and utilized for analysis.

EXAMPLE 2

GPCR FUSION PROTEIN PREPARATION

The design of a GPC6-Fusion Protein construct was accomplished as follows: both the 5' and 3' ends of the rat G protein Gs α (long form; Itoh, H. et al., 83 *PNAS* 3776 (1986)) were engineered to include a HindIII (5'-AAGCTT-3') sequence thereon. Following confirmation of the correct sequence (including the flanking HindIII sequences), the entire sequence was shuttled into pcDNA3.1(-) (Invitrogen, cat. no. V795-20) by subcloning using the HindIII restriction site of that vector. The correct orientation for the Gs α sequence was determined after subcloning into pcDNA3.1(-). The modified pcDNA3.1(-) containing the rat Gs α gene at HindIII sequence was then verified; this vector was now available as a "universal" Gs α protein vector. The pcDNA3.1(-) vector contains a variety of well-known restriction sites upstream of the HindIII site, thus beneficially providing the ability to insert, upstream of the Gs protein, the coding sequence of an endogenous, constitutively active GPCR. This same approach can be utilized to create other "universal" G protein vectors, and, of course, other commercially available or proprietary vectors known to the artisan can be utilized -- the important criteria is that the sequence for the GPCR be upstream and in-frame with that of the G protein.

GPR6-Gs α Fusion Protein construct was made as follows: primers utilized were as follows:

5'-gatcTCTAGAATGCAGGGTGCAAATCCGGCC-3' (SEQ. ID. NO. 3, sense)

5'-ctagGGTACCCGGACCTCGCTGGGAGACCTGGAAC-3' (SEQ.ID.NO. 4, antisense).

The sense and anti-sense primers also contained restriction sites for XbaI and KpnI, respectively.

These restriction sites are available upstream of the HindIII site in the pcDNA3.1(-) vector.

PCR was then utilized to secure the respective receptor sequences for fusion within the Gs α universal vector disclosed above, using the following protocol for each: 100ng cDNA for GPR6 was added to separate tubes containing 2 μ l of each primer (sense and anti-sense), 3 μ L of 10mM dNTPs, 10 μ L of 10XTaqPlus™ Precision buffer, 1 μ L of TaqPlus™ Precision polymerase (Stratagene: #600211), and 80 μ L of water. Reaction temperatures and cycle times were as follows: the initial denaturing step was done at 96°C for seven minutes, and a cycle of 96°C for 30seconds, 55°C for 30 seconds, and 72°C for two minutes was repeated 30 times. A final extension time of ten minutes at 72°C was done for GPR6. PCR products for GPR6 were run on a 1% agarose gel and then purified (data not shown). The purified product was digested with XbaI and KpnI (New England Biolabs) and the desired inserts were isolated, purified and ligated into the Gs universal vector at the respective restriction site. The positive clones were isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. The positive clone for GPR6:Gs α -Fusion Protein was sequenced and made available for the direct identification of candidate compounds. See, SEQ.ID.NO.:5 for nucleic acid sequence and SEQ.ID.NO.:6 for deduced amino acid sequence of GPR6:Gs α -Fusion Protein.

EXAMPLE 3A

ASSESSMENT OF CONSTITUTIVE ACTIVITY USING ADENYLYL CYCLASE ASSAY

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells can contain a scintillant coating that also contains a specific antibody recognizing

cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a protocol for the measurement of changes in cAMP levels in whole cells that express receptors, e.g. GPR6 or GPR6:G α -Fusion Protein.

Transfected cells are harvested approximately twenty-four hours after transient transfection. Media was carefully aspirated off and discarded. 10ml of PBS was gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS were added to each plate. Cells were pipeted off the plate and the cell suspension is collected into a 50ml conical centrifuge tube. Cells were then centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet was carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells were then counted using a hemocytometer and additional PBS is added to give the appropriate number of cells (with a final concentration of about 50×10^4 /well).

cAMP standards and Detection Buffer (comprising 1 μ Ci of tracer [125 I cAMP (50 μ l] to 11 ml Detection Buffer) was prepared and maintained in accordance with the manufacturer's instructions. Stimulation Buffer (preferably prepared fresh) for screening and contained 50ul of Stimulation Buffer, 3ul of test compound (12uM final assay concentration) and 50ul cells, Stimulation Buffer can be stored on ice until utilized. The assay can be initiated by addition of 50ul of cAMP standards to appropriate wells followed by addition of 50ul of PBSA to wells H-11 and H12. 50ul of Stimulation Buffer was added to all wells. DMSO (or selected candidate compounds) were added to appropriate wells using a pin tool capable of dispensing 3ul of compound solution, with a final assay concentration of 12uM test compound and 100ul total assay volume. The cells were then added to the wells and

incubated for 60 min at room temperature. 100ul of Detection Buffer containing tracer cAMP was then added to all the wells. Plates were then incubated an additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well were then extrapolated from a standard cAMP curve that is contained within each assay plate.

GPR6 and GPR6:Gsc α -Fusion-Protein were analyzed as above and verified to be constitutively active, whereby GPR6:Fusion-Protein evidenced about a 4-fold increase in cAMP over GPR6 (*see*, Figure 1). In the context of screening of candidate compounds, when the goal is to identify inverse agonists, agonists or partial agonists, it is preferred that the signal to noise ratio be maximized (especially in the case of screening for inverse agonists). Thus, although it is viable to use GPR6 itself, given the substantial increase in this ratio, the use of the GPR6:Gsc α -Fusion Protein is particularly preferred (although one of ordinary skill in the art is credited with selecting an approach that is based upon the particular needs of the artisan). It is further noted that there does not appear to be an "upper-limit" or "ceiling" for the signal such that despite the increase in signal evidenced in Figure 1, these constructs can also be used for screening to determine agonists of GPR6 (*i.e.*, an agonist will further increase the signal).

EXAMPLE 3B

ASSESSMENT OF CONSTITUTIVE ACTIVITY USING GTP MEMBRANE BINDING SCINTILLATION PROXIMITY ASSAY

Using [³⁵S]GTP γ S binding to measure constitutive activation can be advantageous in that: (a) [³⁵S]GTP γ S binding is generically applicable to all G protein-coupled receptors; and (b) [³⁵S]GTP γ S binding is proximal at the membrane surface, thereby making it less likely to pick-up molecules which affect the intracellular cascade. Preferably, a GPCR:Fusion-Protein is utilized. The assay utilizes the ability of G protein-coupled receptors to stimulate

[³⁵S]GTP γ S binding to membranes expressing the relevant receptors. Therefore, the assay may be used to directly screen compounds at the disclosed GPR6 receptor.

A scintillation proximity assay was utilized to monitor the binding of [³⁵S]GTP γ S to membranes expressing, *e.g.*, the endogenous human GPR6:Gs-Fusion Protein (expressed in 293 cells). In brief, a preferred protocol for the assay is such that the assay was incubated in 20 mM HEPES, pH 7.4, binding buffer (100mM NaCl and 10mM MgCl₂), with 0.6 nM [³⁵S]GTP γ S and 12.5 μ g membrane protein and 0.1 μ M GDP for 60 minutes. The assay plates were then centrifuged at 4000rpm for 15 minutes at room temperature and then subsequently aspirated and counted in a scintillation counter.

Using this assay, enhanced binding of [³⁵S]GTP γ S to membranes prepared from 293 cells expressing the control vector alone or the human GPR6:Gs α -Fusion Protein receptor was comparatively observed. The total protein concentration used in the assay affects the total amount of [³⁵S]GTP γ S binding for each receptor. The c.p.m. differential between the pCMV transfected and the constitutively active GPR6:Gs α -Fusion Protein receptor (at 12.5 μ g/ml) increased from approximately 6000 c.p.m to approximately 11,600 c.p.m. protein concentration.

Results are presented in Figure 2 and evidence that GPR6 receptor (GPR6:Gs α -Fusion Protein) has increased activity as compared to control; this heightened activity is not the result of autocrine stimulation in that the data were obtained from membrane preparations, as opposed to whole cell preparations.

EXAMPLE 4A
DIRECT IDENTIFICATION OF INVERSE AGONISTS AND AGONIST
USING [³⁵S]GTP γ S ASSAY

Although we have utilized endogenous, constitutively active GPR6 for the direct identification of candidate compounds as, e.g., inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. Preferably, then, a GPCR Fusion Protein, as disclosed above, is utilized. When such a protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust direct identification of candidate compounds. The following protocol is preferred:

1. Membrane Preparation

Membranes expressing the GPCR6:Gsc-Fusion Protein (*see* Example 2) and for use in the direct identification of candidate compounds as inverse agonists, agonists or partial agonists were prepared as follows:

(a) Materials

Membrane Scrape Buffer was comprised of 20mM HEPES and 10mM EDTA, pH 7.4; Membrane Wash Buffer was comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4; Binding Buffer was comprised of 20mM HEPES, 100 mM NaCl, and 10 mM MgCl₂, pH 7.4

(b) Procedure

All materials were kept on ice throughout the procedure. Firstly, the media was aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of membrane Scrape Buffer was added to scrape cells; this was followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant was aspirated and the pellet was resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant was then aspirated and the pellet resuspended in Binding Buffer. This was then

homogenized using a Brinkman polytron™ homogenizer (15-20 second bursts until the all material was in suspension). This is referred to herein as "Membrane Protein".

2. Bradford Protein Assay

Following the homogenization, protein concentration of the membranes was determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use is as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a polytron at about 12 x 1,000 rpm for about 5-10 seconds; it is noted that for multiple preparations, the homogenizer should be thoroughly cleaned between homogeneization of different preparations). Membrane protein concentrations are reassessed and normalized to CMV where the optimal protein concentration is between 0.25ug/ul and 0.30ug/ul.

(a) Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard were utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

(b) Procedure

Duplicate tubes were prepared, one including the membrane, and one as a control "blank". Each contained 800ul Binding Buffer. Thereafter, 10ul of Bradford Protein Standard (1mg/ml) was added to each tube, and 10ul of membrane Protein was then added to just one tube (not the blank). Thereafter, 200ul of Bradford Dye Reagent was added to each tube, followed by vortex of each. After five (5) minutes, the tubes were re-vortexed and the material therein was transferred to cuvettes. The cuvettes were then read using a CECIL 3041 spectrophotometer, at wavelength 595.

3. Direct Identification Assay

(a) Materials

GDP Buffer consisted of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 uM GDP (final concentration of GDP in each well was 0.1 uM GDP); each well comprising a candidate compound, had a final volume of 200ul consisting of 100ul GDP Buffer (final concentration, 0.1uM GDP), 50ul Membrane Protein (12.5ug) in Binding Buffer, and 50ul [³⁵S]GTPγS (0.6 nM) in Binding Buffer (2.5 ul [³⁵S]GTPγS per 10ml Binding Buffer).

(b) Procedure

Candidate compounds (Tripos, Inc., St. Louis, MO) were received in 96-well plates (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPR6:Gα-Fusion Protein, as control), were homogenized briefly until in suspension. Protein concentration was then determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) was then diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5ug/well). Thereafter, 100 ul GDP Buffer was added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool was then used to transfer 5 ul of a candidate compound into such well (*i.e.*, 5ul in total assay volume of 200 ul is a 1:40 ratio such that the final screening concentration of the candidate compound is 10uM). Again, to avoid contamination, after each transfer step the pin tool was rinsed in three reservoirs comprising water (1X), ethanol (1X) and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper towels and kimwipes™. Thereafter, 50 ul of Membrane Protein was added to each well (a control well comprising membranes without the GPCR Fusion Protein is also utilized), and pre-incubated for 5-10 minutes at room

temperature (the plates were covered with foil in that the candidate compounds obtained from Tripos are light sensitive). Thereafter, 50 ul of [35 S]GTP γ S (0.6 nM) in Binding Buffer was added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay was then stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates were then aspirated with an 8 channel manifold and sealed with plastic plate covers. The plates were then read on a Wallac 1450 using setting "Prot. #37" (as per manufacturer instructions).

EXAMPLE 4B DIRECT IDENTIFICATION OF "LEADS"

We believe that it is important to note that the following results have been obtained using an *orphan* receptor; as the data support, it is possible, using the techniques disclosed herein, to directly identify candidate compounds that modulate the orphan receptor as inverse agonists, agonists and partial agonists, directly from a primary screen; indeed, the methods disclosed herein are sensitive enough to allow for direct identification of both inverse agonist and agonist modulators on the same assay plate.

The initial or "primary" screen designed to directly identify, *e.g.*, human GPR6 receptor inverse agonists, consisted of the membrane-based GTP γ S binding assay of Example 4A utilizing membranes prepared from 293 stable cells. Candidate compounds directly identified as inhibiting receptor-mediated increases in GTP γ S as set forth below were considered active "leads". Primary assay leads were then re-tested in the same assay to reconfirm their inverse agonist activity. If primary assay hits were reconfirmed active (50% or greater inhibition), and therefore directly identified as, *e.g.*, an inverse agonist, additional candidate compounds were synthesized based upon the structures of the reconfirmed hits

(geared towards, *e.g.*, improvement in the characteristics of the compounds) whereby the directed library compounds (Arena Pharmaceuticals, Inc., San Diego CA) were then evaluated. The last step in secondary assay evaluation was to determine if test compounds were capable of inhibiting cAMP accumulation (*i.e.*, adenylate cyclase-based assay, disclosed below in Example 4C). This final assay confirms that the directly identified compounds retained inverse agonist properties.

A representative screening assay plate (96 well format) result is presented in Figure 3. Each bar represents the results for a different compound in each well, plus the GPR6:Gs Fusion Protein. The representative results presented in Figure 3 also provide standard deviations based upon the mean results of each plate ("m") and the mean plus two standard deviations ("m+2sd") and the mean minus two standard deviations ("m-2sd"). Our arbitrary preference for selection of inverse agonists as "leads" from the primary screen involves selection of candidate compounds that reduce the per cent response by at least the mean plate response, minus two standard deviations. Based on this selection process, the candidate compounds in the following wells were directly identified as putative inverse agonists to the GPR6 receptor: A7; B2; F6; G6 and H6. Further evaluation (using a non-GPR6 receptor) of compounds designated in wells A7, B2, F6 and G6 indicated that these compounds were non-specific to GPR6:Gs-Fusion Protein receptor and thus may instead act to uncouple the G protein from the GPR6 receptor (data not shown). Thus, the candidate compound of well H6, designated "ARE112" was selected for further evaluation.

It is preferred that following such direct identification, IC_{50} (inverse agonist) or EC_{50} (agonist) values be determined; those having ordinary skill in the art are credited with utilizing

IC₅₀ and EC₅₀ assay protocols of choice. Figure 4 provides a representative IC₅₀ curve for compound ARE112 using the assay protocol of Example 4A.

EXAMPLE 4C CYCLIC AMP CONFIRMATION ASSAY

Using an independent assay approach to provide confirmation of a directly identified candidate compound as set forth above, it is preferred that a confirmation assay then be utilized. In this case, the preferred confirmation assay is membrane-based cyclic AMP (cAMP) assay.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) was utilized for confirmation of candidate compounds directly identified as inverse agonists and agonists to endogenous, constitutively activated orphan GPCRs in accordance with the following protocol.

Transfected stable cells were harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCl₂. Homogenization was performed on ice using a Brinkman Polytron™ for approximately 10 seconds. The resulting homogenate was centrifuged at 20,000 rpm for 20 minutes at 4°C. The resulting pellet was then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 20,000 rpm for 20 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet is slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4, 100mM NaCl and 10mM MgCl₂, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 μ Ci of tracer [125 I] cAMP (50 μ l] to 11 ml Detection Buffer) were prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 20mM HEPES, pH 7.4, 100mM NaCl, 10mM MgCl₂, 20mM phosphocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μ M GTP (Sigma), 0.2 mM ATP (Sigma) and 0.6mM isobutyl-methyl xanthine (IBMX); Assay Buffer can be stored on ice until utilized.

Candidate compounds identified as per above (if frozen, thawed at room temperature) were added to plate wells (3 μ l/well; 12 μ M final assay concentration), together with 50 μ l Membrane Protein (30 μ g/well) and 50 μ l of Assay Buffer. This admixture was then incubated for 30 minutes at room temperature, with gentle shaking.

Following the incubation, 100 μ l of Detection Buffer was added to each well, followed by incubation for 2-20 hours. Plates were subsequently aspirated and then counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

The following Table A lists the IC₅₀ values determined utilizing the foregoing cAMP assay.

Table A

Assay Number For Compound ARE112	IC ₅₀ Values (nM) cAMP	Maximum (c.p.m.)	Minimum (c.p.m.)
1	88.3	138.1	4.3
2	77.39	128.5	2.7
3	99.00	125.7	3.2

Preferably, for IC₅₀ determinations, the dose response range at the maximum is between 80 and 120 percent control ("% control"), and at the minimum between 20 and -20 percent control, although such parameters can be a matter of choice for the artisan, depending upon the particular needs of the artisan.

EXAMPLE 5 SCREENING OF DIRECTED LIBRARY

Based upon the foregoing results, structure activity analysis of the ARE112 compound suggested that a series of derivatives of ARE112, N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,3-dithiazol-3-ylidene), as well as derivatives of ARE111 N-(2-thioxo-imidazolidine-1-carbothioyl) would exhibit similar GPR6 inverse agonist activity and selectivity. A directed library series of derivatives of N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,3-dithiazol-3-ylidene) and of N-(2-thioxo-imidazolidine-1-carbothioyl) were synthesized (*see* Examples 8 and 9, *infra*). IC₅₀ values were determined using the assays indicated below, by taking the mean values of the number of assays (placed in brackets), +/- the standard deviation. These, too were assessed using the above protocols, and results are summarized below in Table B:

Table B

Compound Identifier	IC ₅₀ Values GTP Assay Example 4A (μ M)	IC ₅₀ Values Cyclic AMP Assay Example 4C (μ M)
ARE111	2.79 +/- 1.14 (4)	1.96 +/- 2.51 (4)
ARE112	0.42 +/- 0.24 (12)	0.10 +/- 0.07 (5)
ARE113	100 +/- 110 (4)	N/D
ARE114	0.44 +/- 0.46 (3)	0.17 +/- 0.01 (2)
ARE115	1.57 +/- 1.748 (5)	3.65 +/- 3.45 (8)
ARE116	0.57 +/- 0.24 (7)	0.17 +/- 0.05 (5)
ARE117	200 (3)	N/D
ARE118	0.65 +/- 0.67 (3)	0.37 +/- 0.18 (6)
ARE119	0.45 +/- .12 (3)	1.97 +/- 1.53 (3)
ARE120	0.64 +/- 0.25 (6)	0.27 +/- .02 (5)
ARE121	122 +/- 100 (5)	55 +/- 96 (4)
ARE122	0.83 +/- 0.12 (2)	0.21 +/- 0.19 (2)
ARE123	56 +/- 95 (4)	51 +/- 98 (4)
ARE124	0.31 +/- 0.11 (4)	0.40 +/- 0.25 (3)
ARE125	3.8 +/- 3.5 (3)	120 +/- 100 (5)
ARE126	0.79 +/- 0.08 (3)	0.14 +/- 0.04 (2)
ARE127	1.25 +/- 0.22 (3)	0.48 +/- 0.40 (4)
ARE1128	0.37 +/- 0.02 (2)	0.20 +/- 0.13 (6)

ARE129	3.19 +/- 3.63 (3)	2.62 +/- 4.26 (4)
ARE130	0.22 +/- 0.22 (3)	0.24 +/- 0.19 (5)
ARE131	43 +/- 87 (5)	200 (4)
ARE132	0.35 +/- 0.35 (2)	0.10 +/- 0.01 (2)
ARE133	0.11 +/- 0.11 (4)	0.17 +/- 0.07 (5)
ARE134	0.41 +/- 0.26 (6)	0.19 +/- 0.19 (4)
ARE135	100 +/- 130 (2)	0.71 +/- 0.74 (4)
ARE136	0.17 +/- 0.07 (3)	0.17 +/- 0.13 (5)
ARE137	200 (3)	100 +/- 100 (2)
ARE138	0.45 +/- 0.16 (3)	0.13 +/- 0.07 (3)
ARE139	0.26 +/- 0.22 (3)	4.52 +/- 3.14 (3)
ARE140	0.13 +/- 0.06 (3)	0.19 +/- 0.21 (5)
ARE143	68.29 +/- 0.11 (3)	160 +/- 0.09 (5)
ARE144	0.25 +/- 0.03 (3)	0.11 +/- 0.05 (2)
ARE148	0.46 +/- 0.27 (4)	0.35 +/- 0.21 (5)
ARE149	2.43 +/- 2.12 (4)	5.83 +/- 4.95 (3)
ARE150	0.33 +/- 0.07 (2)	0.10 +/- 0.19 (3)
ARE151	200 (3)	200 (3)
ARE152	0.1897 (3)	N/D
ARE153	2.46 +/- 0.42 (3)	N/D
ARE154	200 (3)	80 +/- 103 (3)
15F155	6.56 +/- 2.0 (3)	0.85 +/- 0.24 (3)

ARE156	0.67 +/- 0.11 (3)	0.133 +/- 0.06 (2)
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N/D = data not yet determined

EXAMPLE 6
***IN VIVO* ANALYSIS**

**1. Food/Water Intake and Body Weight in
24-Hour Food-Deprived Animals**

The profile of ARE112 from the *in vitro* functional assays suggested that this compound exhibits selective GPR6 inverse agonist properties. An *in vivo* assessment of GPR6 inverse agonist was accomplished by determining the effects of ARE112 on food intake after food deprivation in rats. Food deprivation was used to induce higher than normal eating behavior (*e.g.*, control/vehicle-treated animals were hyperphagic).

The animals (male Sprague-Dawley rats were used for the following experiments) were food deprived for 24 hr, and then injected intraperitoneally (IP) with 0, 6.75, 13.5, 27 and 54mg/kg of compound ARE112. After 30 min, rats were introduced to standard rat chow pellets and observed thereafter for a period of 6.5 hours post-injection.

Data evidence that animals treated IP with compound ARE112 exhibit decreased food intake, water intake and body weight gain. In Figure 5A, at 1.5 hours after injection, vehicle treated animals consumed about 6grams of food, while ARE112 treated (54mg/kg) consumed 3g of food. As time progressed, the data indicate that vehicle-treated ate substantially more food (up to 14g at 6.5 hours post-injection), while the ARE112 treated, particularly animals treated with 54 mg/kg of ARE112, consumed 4 g (*see*, Figure 5A). Four and 5 fold decreases in water intake at doses of 27 and 54 mg/kg, respectively, were also evidenced by the data, which appear to parallel the decreased amount of food eaten. (*See*, Figure 5B). Vehicle treated rats evidenced a body weight gain of 20 g, whereas ARE112 treated rats

evidenced the following: 13.5 mg/kg treatment - 11g weight gain; 27 and 54 mg/kg treatment - no weight gain (*see*, Figure 5C).

2. Basal Food/Water Intake and Body Weight in Non-Food Deprived Animals

Animals were also observed during their most active period (dark cycle), and both basal food and water intake were measured. In this test, animals were not deprived of food but were instead observed for normal activity.

Animals were administered ARE112 at 0, 6.75, 13.5, 27 and 54 mg/kg, IP 30 min prior to the beginning of their dark cycle (*i.e.* 6:30 pm) and were then exposed to standard rat chow pellets (*i.e.* 30 min after compound administration) and observed for a period of 15.5 hr post administration. Data, presented in Figure 6A, evidence that animals administered with ARE112 did not eat as much as animals administered vehicle. For example, the vehicle treated animals consumed 9 g of food over a period of 4 hrs, whereas animals treated with dose of 13.5mg/kg and 54 mg/kg consumed less than half this amount over this same period (4 and 2 g of food, respectively). Similar to the food-deprived rats, the non-deprived rats also exhibited a decrease in water intake and body weight gain. (*See*, Figures 6B and 6C).

Long-term effects (60 days) of ARE112 were also examined. Animals (treatment, n= 4; control, n = 5) were treated once a day intraperitoneally with ARE112 for 22 days and assessed for a period of 60 days. On days 1 to 3, animals treated with dose of 13.5mg/kg initially lost body weight and between day 4 and day 31, animals gradually gained weight, although still weighing less than vehicle treated animals. After day 31 and through day 60, the data support the position that there was a significant difference in body weight between the treated animals and the vehicle animals. The data support the conclusion that daily,

repeated administration of ARE112 (at 13.5mg/kg) induces a long-term decrease in body weight in non-food deprived rats. *See*, Figure 11.

3. Intracerebroventricular (ICV) Administration of ARE112 on Food-Deprived Animals

a. Surgery

Animals were prepared with an ICV cannula aimed above the lateral ventricle. For this surgery, animals were placed under general anesthesia using continuous inhalation of isoflurane and secured in a Kopf stereotaxic instrument. Surgery was performed in a dedicated surgery room, using sterile instruments, surgical gloves and aseptic procedures to prevent clinical infections. The surgical site was shaved and disinfected with betadine solution and alcohol. Animals were observed continuously for the level of anesthesia by testing for the animals' responses to tail- or paw-pinch. A cannula made of 23 gauge stainless steel tubing (7mm long) was lowered to a point 1mm above the ventricle, using coordinates: A/P -0.6 mm from bregma, M/L +/- 2.0 mm from bregma, D/V 3.2 mm below skull surface. The guide was anchored to the skull with three stainless steel screws and dental cement. Coordinates were based on stereotaxic atlas such as Paxinos and Watson stereotaxic atlas (Paxinos, G. and Watson, C, The Rat Brain, New York, Academic Press, 1982). After cannula implantation, a 30-gauge stainless steel dummy stylet was inserted into the cannula. At the conclusion of surgery, a heat source (heat lamp directed towards one half of recovery cage) was used to maintain body temperature while the animals recovered from anesthesia. Animals were allowed at least one week of recovery after surgery before ICV injection of compound was performed.

b. Administration of ARE112

Animals were food-deprived for 24 hours prior to administration of the compound.

For ICV injection, the dummy stylet was removed from the implanted cannula, and a 30-gauge stainless steel injector cannula containing ARE112 suspension in a 45% cyclodextrin solution was inserted to a depth 1.5mm beyond the ventral tip of the implanted cannula. The other (non-inserted) end of the injector cannula was attached to 60 cm of PE10 tubing containing the compound suspension, which was attached at the free end of tubing to a 25 μ l Hamilton syringe. Ten microliters of ARE112 suspension (containing, 0, 25, 50, and 100nmol) were then delivered via gentle and even mechanical pressure to the plunger of the Hamilton syringe. The volume of injection was verified by marks on the PE 10 tubing previously calibrated with a 10 μ l Hamilton syringe. At the conclusion of injection, any fluid observed from the dorsal tip of the implanted cannula upon withdrawal of the injector cannula was noted, and the dummy stylet was inserted into the implanted cannula.

Data evidence that after two hours post-administration of ARE112 at all doses, animals consumed substantially less food (about 6 fold less food was consumed). After three hours, the vehicle rat consumed about 2.5 grams of food, while ARE112 treated rats consumed about 1.0 grams or less. *See*, Figure 7A. Treated animals (at 25 and 50 nmol) drank a comparable amount of water as the vehicle, *i.e.*, about 17 grams. At higher doses (e.g., 100 nmol), about less than half that amount was consumed. *See*, Figure 7C. The data evidence, consistent with the data developed using IP administration, that at a dose of 100nmol of ARE112, the ICV treated animal gained substantially less weight (e.g., 5grams) when evaluated against the vehicle, which gained about 12 grams. *See*, Figure 7C.

4. Effect of ARE112 on Motor Function

The effect of ARE112 on motor function was also examined. Motor function was assessed by using automated locomotor activity cages. Animals were placed in a standard

rodent cage surrounded by photocell, which allowed for automated recording of motor activity. Animals were under no motivational constraints and were free to move around the cage.

Male Sprague-Dawley rats ($n = 4-9$ per dose) were administered ARE112 (IP) prior to placement into in locomotor activity cages. Data are presented in Figure 8. Based upon the data, it can be concluded that ARE112 does not affect locomotor activity where animals were exposed to locomotor activity cages for 1.5 hour immediately after injection of ARE112. While the data support the conclusion that ARE112 decreases locomotor activity in rats 16 hours post-injection (see, Figure 8), thus indicating that ARE112 has some sedative activity, (e.g., the animals appear relaxed and demonstrate little to no anxiety-like behavior), this sedative activity is mild and cannot, in and of itself, account for the decrease in food intake.

As further evidence of this mild sedative activity, animals were measured to determine their startle reflexes. In this assay, ARE112 was orally administered in non-food deprived rats 4.5 hours prior to testing. Animals were subjected to a pre-pulse of 12db followed by a 120db pulse and subsequently measured for the height in which the animals jumped. Figure 12 shows the average startle amplitude of administered rats (i.e., at 6.75, 13.5 and 54mg/kg). Treated rats at 13.5 and 54mg/kg did not jump as high, as compared to the vehicle and rats treated at the low dose of 6.75mg/kg, in response to the pulse. This data further suggests that at a higher dosage of ARE112, animals demonstrate a mild sedative activity.

5. Oral Availability: ARE112

Based upon the *in vivo* data developed, oral bioavailability of compound ARE112 was determined. The compound was administered by oral gavage at doses ranging from 6.75 to

54 mg/kg. The data presented in Figures 9A and 9B support the conclusion that oral administration of ARE112 also decreases food intake in both food-deprived and non-food deprived rats. The effect of ARE112 was dose-dependent and comparable to the effect observed after IP administration. In Figure 9A, rats were deprived 24 hours prior to oral administration of the compound. In this assay, the vehicle-treated rats at 2.5 hours consumed about 6 grams of food while injected rats; particularly rats administered with 27 and 54mg/kg of ARE112, ate about 6 and 4 grams, respectively. As time progressed, the vehicle rat consumed significantly more, about 14 grams at 8 hours post-administration, while treated rats (at 27 and 54 mg/kg) consumed about 8 grams and 6grams, respectively. (See, Figure 9A).

In a second assay, rats were treated with ARE112 by oral gavage but were not food deprived. Data evidence an even greater decrease in food intake, such that at 18 hours post administration of the compound, the vehicle rats had consumed about 15 grams of food while the injected rats (at all doses) ate 5grams or less; about a three fold decrease in food consumption when treated with compound ARE112. (See, Figure 9B). These data support the conclusion that ARE112 is orally active.

6. Assessment of Other Compounds.

Several other GPR6 inverse agonists were also assessed under 24-hour food deprived conditions, with PO administration. The analogs listed below were tested at 200 μ mol/kg, which is equivalent to 54mg/kg. In addition, ARE114 was also assessed at 100 μ mol/kg (27 μ mol/kg). Data are summarized below in Table C:

Table C

Analogs	Cumulative Food Intake (g) (8hr post administration)	Cumulative Water Intake (g) (6hr post administration)	Body Weight Gain (g) (6hr post administration)
Vehicle	14.5	22.9	20.3
ARE114 (100 μ mol/kg)	10.8	15.3	13.6
ARE114 (200 μ mol/kg)	8.68	10.6	6.18
ARE120 (200 μ mol/kg)	9.88	18.5	11.4
ARE128 (200 μ mol/kg)	7.93	8.5	4.03

In a second assay, tested under the same conditions, several other analogs were assessed at 100 μ mol/kg. Data are summarized below in Table D.

Table D

Analogs (100 μ mol/kg)	Cumulative Food Intake (g) (8hr post administration)	Cumulative Water Intake (g) (6hr post administration)	Body Weight Gain (g) (6hr post administration)
Vehicle	14.0	19.25	19.25
ARE112	8.1	10.5	6.25
ARE130	9.1	9.5	9.5
ARE135	13.5	19.5	19.5
ARE136	9.0	15.25	11.0
ARE140	9.6	20.0	14.6

In Figure 10, rats were deprived 24 hours prior to oral administration of the compound. In this assay, analogs ARE130, ARE135, ARE136, and ARE140, were administered at a dose of 100 μ mol/kg. Three analogs, particularly, ARE130, ARE136 and ARE140 evidenced a slow intake of food (*e.g.*, about 1 to 1.5 grams every two hours) over an eight hour period post-administration; while the vehicle rat consumed about 2 to 2.5 grams food every two hours. Similar to the vehicle rat, analog ARE135, an opened ring structure, evidenced that over an eight hour period post-administration the rats increasingly consumed about 2.5 grams every two hours. (*See*, Figure 10A). Furthermore, the body weight of the vehicle rat and administered rats with analog ARE135 gained about 19.5 grams. On the other hand, the closed ring structures evidenced a decrease in body weight gain as follows: ARE112-6 grams, ARE130-9 grams, ARE136-11 grams and ARE140-14 grams. *See*, Figure 10C.

The treated rats, particularly ARE130 and ARE136, drank less amount of water compared to the vehicle animal, *i.e.*, about 10 grams and 4 grams less, respectively; while analogs ARE135 and ARE140 drank a comparable amount (*i.e.*, about 19 grams). *See*, Figure 10B. These data suggests that the closed ring structures, preferably ARE112, ARE130, ARE136 and ARE140; more preferably ARE112 and ARE130; and most preferably ARE112, are specific to the G protein-coupled receptor six.

Table E below lists several IC₅₀ values for the analogs of ARE112. IC₅₀ values were derived using the GTP Assay as disclosed in Example 4A. At low concentrations of analogs ARE130, ARE136 and ARE140 GPR6 is activated, thus stimulating the conversion of GTP to GDP. This data supports the suggestion that closed ring structures are selective inverse agonists for GPR6.

Table E

Analogs	IC ₅₀ Values (μM)
ARE130	022 +/- 022 (3)
ARE135	100 +/- 137 (2)
ARE136	0.17 +/- 0.07 (3)
ARE140	0.17 +/- 0.13 (5)

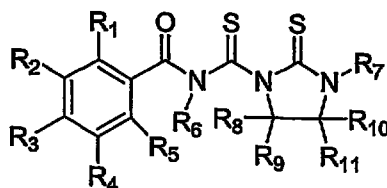
EXAMPLE 7 GPR6 INVERSE AGONISTS

Based upon the patent disclosure and the information provided herein, one of ordinary skill in the art is credited with the ability to directly identify candidate compounds as inverse agonists, agonists and partial agonists to GPR6. Most preferably, these will be small molecule compounds that have not evidenced these characteristics (*i.e.*, selective for GPR6) prior to such direct identification. For agonists, the objective in the screening is to find small molecules that increase the measured signal.

Below, we disclose our most preferred small molecule GPR6 inverse agonists. It is recognized that various stereoisomeric forms of the compounds disclosed herein may exist. It is intended that the present invention include racemates, individual enantiomers, and mixtures thereof.

1. Open Chain Aryl Series

As a first series of GPR6 inverse agonists, disclosed are "open chain aryls" represented structurally as follows (note: if the selection of one or more of R⁸, R⁹, R¹⁰, and R¹¹ results in an asymmetric or diastereomeric molecule, then the racemic mixtures, the diastereomeric mixtures and each of the separated (+) and (-) enantiomers or diastereomers are within the scope of the disclosed series, and within the scope of the claims to follow):



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN , $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$ wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl, and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position on said aryl, each said position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring, said aryl ring being substituted at two adjacent positions on said aryl ring, then said two adjacent

positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N and S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂;

or

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

The following provisos, preferentially noted, may apply whereby when R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are all H, then at least one of R^1 , R^2 , R^3 and R^4 is other than H; and when R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are all H, then R^3 is not Cl, CH_3 , or OCH_3 ; and when R^1 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are all H, then R^2 , R^3 , and R^4 are not OCH_3 .

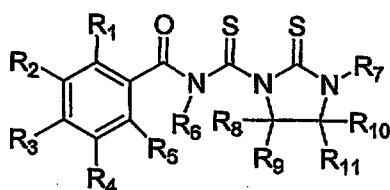
An "aryl moiety" can be a 5 or 6 membered aromatic heterocyclic ring (containing up to four hetero atoms independently selected from N, O, or S) or a six membered aromatic non-heterocyclic ring or a polycycle;

Examples of suitable C_{1-8} alkyl groups include, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl. Throughout this specification, the term "alkylaryl" is intended to mean alkyl moieties having an aryl moiety attached thereto, for example benzyl groups.

Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl,

thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazoliny and benzothienyl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented as follows:



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN, $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$ wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl, and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position on said aryl, each said position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$,

COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring, said aryl ring being substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N and S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN,

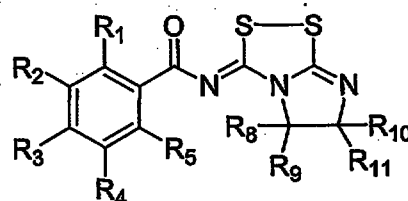
COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅,
 COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅,
 CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂;
 or

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

2. Closed chain aryl series

A second series of GPR6 inverse agonists are "closed chain aryls" represented structurally as follows:



wherein R¹, R², R³, R⁴, and R⁵ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴,
 NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹²,

OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R¹, R², R³, R⁴, and R⁵ can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R¹² is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, (CH₂)_nNR¹³R¹⁴, (CH₂)_mSO₃H, and (CH₂)_mCO₂H wherein n is 2 through 6 and m is 1 through 6;

R¹³ and R¹⁴ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₂₋₈ alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH₂aryl, wherein each said aryl group or said aryl portion of said CH₂aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃,

OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ may form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃,

OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} ,
 OCF_3 , OCOCH_3 , OCOC_2H_5 , OCOC_3H_7 , OCOC_4H_9 , OSO_2CH_3 ,
 $\text{OSO}_2\text{C}_2\text{H}_5$, $\text{OSO}_2\text{C}_3\text{H}_7$, $\text{OSO}_2\text{C}_4\text{H}_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 ,
 SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , SCOCH_3 , SCOC_2H_5 ,
 SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$, $\text{SO}_3\text{C}_4\text{H}_9$,
 SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$,
 $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN ,
 COOCH_3 , COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 ,
 COSC_3H_7 , COSC_4H_9 , CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 ,
 $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 , $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$,
 and

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{SCH}_2\text{S}$, $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl;

The following provisos, preferentially noted, may apply whereby when R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are all H, then at least one of R^1 , R^2 , R^3 and R^4 is other than H; and when R^1 , R^2 , R^4 , R^5 ,

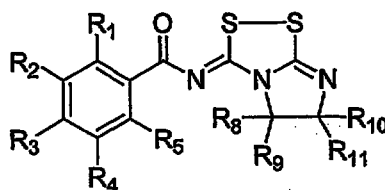
$R^6, R^7, R^8, R^9, R^{10}$, and R^{11} are all H, then R^3 is not Cl, CH_3 , or OCH_3 ; and when $R^1, R^5, R^6, R^7, R^8, R^9, R^{10}$, and R^{11} are all H, then R^2, R^3 , and R^4 are not OCH_3 .

An "aryl moiety" can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

Examples of suitable C_{1-8} alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazolinyl and benzothienyl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented as follows:



wherein R^1, R^2, R^3, R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN , $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR^{13}R^{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$ wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$,

NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ may form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂,

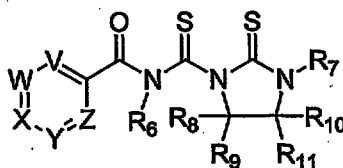
NHCOH , NHCOCH_3 , NHCOC_2H_5 , NHCOC_3H_7 , NHCOC_4H_9 ,
 NHSO_2CH_3 , $\text{NHSO}_2\text{C}_2\text{H}_5$, $\text{NHSO}_2\text{C}_3\text{H}_7$, $\text{NHSO}_2\text{C}_4\text{H}_9$, OH , OCH_3 ,
 OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_{11} , OC_6H_{13} ,
 OCF_3 , OCOCH_3 , OCOC_2H_5 , OCOC_3H_7 , OCOC_4H_9 , OSO_2CH_3 ,
 $\text{OSO}_2\text{C}_2\text{H}_5$, $\text{OSO}_2\text{C}_3\text{H}_7$, $\text{OSO}_2\text{C}_4\text{H}_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 ,
 SC_5H_{11} , SC_6H_{13} , SCF_3 , SCOCH_3 , SCOC_2H_5 ,
 SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$, $\text{SO}_3\text{C}_4\text{H}_9$,
 SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$,
 $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN ,
 COOCH_3 , COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 ,
 COSC_3H_7 , COSC_4H_9 , CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 ,
 $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 , $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$,
 and

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent
 positions on said aryl ring, then said two adjacent positions can be joined by a
 chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 ,
 $\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{SCH}_2\text{S}$, $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a
 bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9}
 alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl;

3. Open chain 6 membered heteroaryl series

A third series of GPR6 inverse agonists are "open chain 6 membered heteroaryls" represented structurally as follows:



wherein at least one of V, W, X, Y and Z is selected from N and each of V, W, X, Y, and Z that is/are not N are independently selected from CR¹, CR², CR³, CR⁴, and CR⁵, with the proviso that at least two of V, W, X, Y and Z are other than N;

R¹, R², R³, R⁴, and R⁵ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴, NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹², OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R¹, R², R³, R⁴, and R⁵ can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure;

R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a

chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅,

CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂,
and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl;

An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

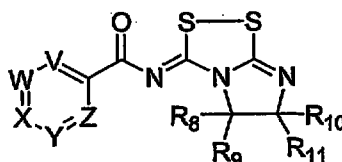
Examples of suitable C₁₋₈ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazolinyl and benzothieryl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented by the foregoing open chain 6 membered heteroaryl series.

4. Closed chain 6 membered heteroaryl series.

A fourth series of GPR6 inverse agonists are "closed chain 6 membered heteroaryls" represented structurally as follows:



wherein at least one of V, W, X, Y and Z is selected from N and each of V, W, X, Y, and Z that is/are not N are independently selected from CR¹, CR², CR³, CR⁴, and CR⁵, with the proviso that at least two of V, W, X, Y and Z are other than N;

R¹, R², R³, R⁴, and R⁵ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴, NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹², OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 ,

SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃,

SCOCH_3 , SCOC_2H_5 , SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$,
 $\text{SO}_3\text{C}_4\text{H}_9$, SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$,
 $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN , COOCH_3 ,
 COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 , COSC_3H_7 , COSC_4H_9 ,
 CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 , $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 ,
 $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$, and

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on
 said aryl ring, then said two adjacent positions can be joined by a chain selected from
 CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S ,
 $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9}
 alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl;

An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4
 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-
 heterocyclic ring or a polycycle;

Examples of suitable C_{1-8} alkyl groups include but are not limited to methyl, ethyl, n-propyl,
 i-propyl, n-butyl, and t-butyl;

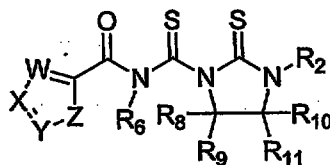
Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl,
 furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl,

tetrazolyl, thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazolinyl and benzothiényl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented by the foregoing closed chain 6 membered heteroaryl series.

5. Open chain 5 membered heteroaryl (sub-series a).

A fifth series of GPR6 inverse agonists are "open chain 5 membered heteraryls" represented structurally as follows:



wherein Z is selected from NR⁴, O and S;

W, X, or Y are independently selected from N, CR¹, CR², and CR³, with the proviso that when Z is O and Y is N, then W is CR¹ and X is CR²;

R¹, R², and R³ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴, NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹², OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^4 is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, cycloalkylalkyl, or aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} ,

SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅,

CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂,
and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

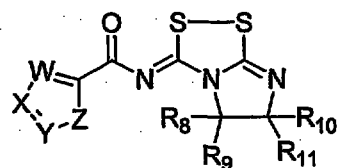
Examples of suitable C₁₋₈ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalyl, quinazolinyl and benzothienyl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented by the foregoing open chain 5 membered heteroaryl series.

6. Closed chain 5 membered heteroaryl (sub-series a)

As a sixth series of GPR6 inverse agonists, disclosed are "closed chain 5 membered heteroaryl sub-series a" represented structurally as follows:



wherein Z is selected from NR⁴, O and S;

W, X, or Y are independently selected from N, CR¹, CR², and CR³, with the proviso that when Z is O and Y is N, then W is CR¹ and X is CR²;

R¹, R², and R³ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴, NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹², OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R¹, R², R³, R⁴, and R⁵ can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure;

R⁴ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, COR⁵, CSR⁵, and SO₂R⁵;

R⁵, R⁶ and R⁷ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R⁶ and R⁷ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, $(CH_2)_mCO_2H$ wherein n is 2 through 6 or m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or

R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up

to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

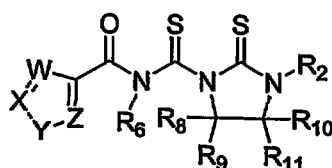
Examples of suitable C₁₋₈ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalyl, quinazolinyl and benzothienyl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented by the foregoing closed chain 5 membered heteroaryl series.

7. Open chain 5 membered heteroaryl (sub-series b)

As a seventh series of GPR6 inverse agonist, disclosed are "open chain 5 membered heteroaryl sub-series b" represented structurally as follows:



wherein Y is selected from NR⁴, O or S;

W, X, or Z are each independently selected from N or CR¹, CR², or CR³, with the proviso that when Y is O and Z is N, then W is CR¹ and X is CR²;

R¹, R², and R³ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴, NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹²,

OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R¹, R², R³, R⁴, and R⁵ can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R⁴ is H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, COR⁵, CSR⁵, and SO₂R⁵;

R⁵, R⁶ and R⁷ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R⁶ and R⁷ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl

R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R¹² is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, (CH₂)_nNR¹³R¹⁴, (CH₂)_mSO₃H, and (CH₂)_mCO₂H, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or

R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$,
and

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$,

$\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{SCH}_2\text{S}$, $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

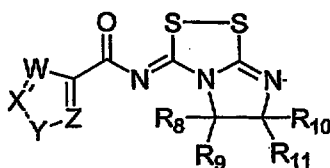
Examples of suitable C_{1-8} alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalyl, quinazolinyl and benzothienyl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented by the foregoing open chain 5 membered heteroaryl series.

8. Closed chain 5 membered heteroaryl (sub-series b)

As an eighth series of GPR6 inverse agonists, disclosed are "closed chain 5 membered heteroaryl sub-series b" represented structurally as follows:



wherein Y is selected from NR⁴, O or S;

W, X, or Z are each independently selected from N or CR¹, CR², or CR³, with the proviso that when Y is O and Z is N, then W is CR¹ and X is CR²;

R¹, R², and R³ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴, NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹², OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R¹, R², R³, R⁴, and R⁵ can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R⁴ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, COR⁵, CSR⁵, and SO₂R⁵;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} ,

OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃,

OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} ,
 OCF_3 , OCOCH_3 , OCOC_2H_5 , OCOC_3H_7 , OCOC_4H_9 , OSO_2CH_3 ,
 $\text{OSO}_2\text{C}_2\text{H}_5$, $\text{OSO}_2\text{C}_3\text{H}_7$, $\text{OSO}_2\text{C}_4\text{H}_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 ,
 SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , SCOCH_3 , SCOC_2H_5 ,
 SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$, $\text{SO}_3\text{C}_4\text{H}_9$,
 SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$,
 $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN ,
 COOCH_3 , COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 ,
 COSC_3H_7 , COSC_4H_9 , CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 ,
 $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 , $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$,
 and

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , and $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-3} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

Examples of suitable C₁₋₈ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

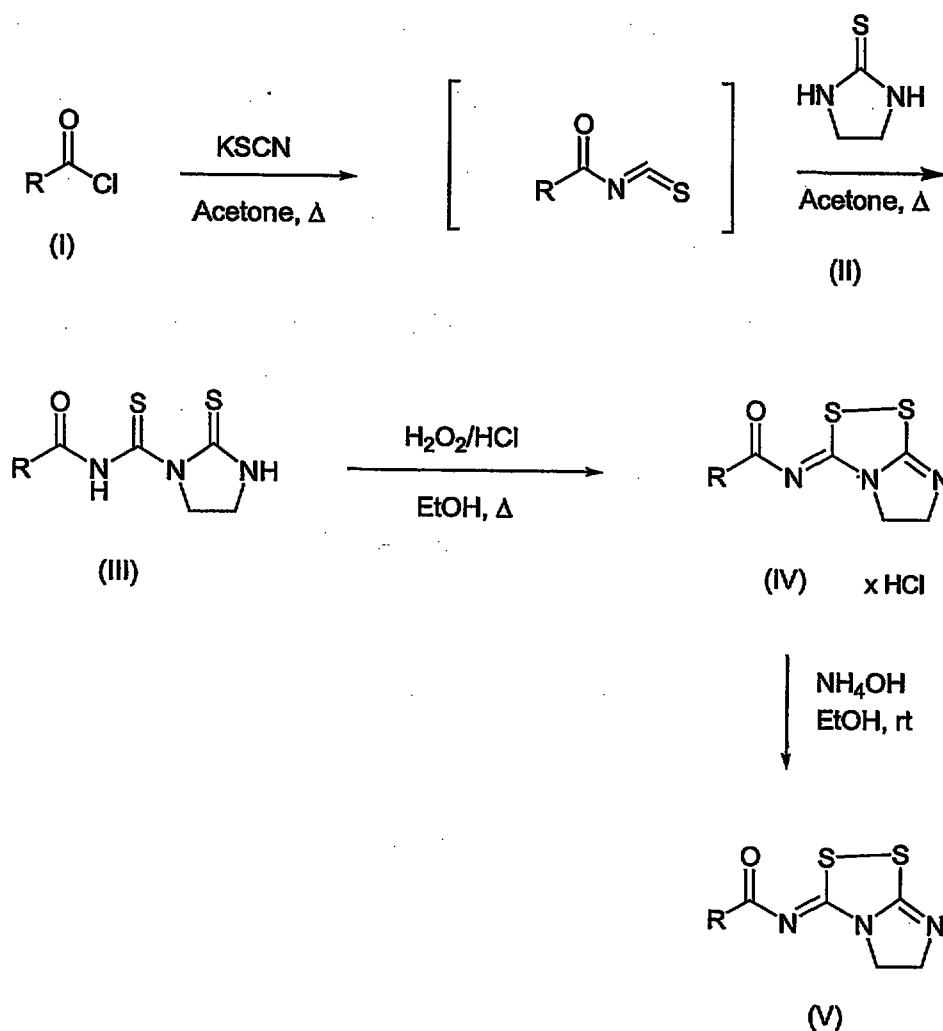
Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalyl, quinazolinyl and benzothienyl.

Further disclosed is a method of modulating the GPR6 receptor by contacting said receptor with a small molecule structurally represented by the foregoing closed chain 5 membered heteroaryl sub-series

EXAMPLE 8A

SYNTHETIC APPROACHES

The compounds disclosed in this invention may be readily prepared according to a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. In the general syntheses set forth below, the labeled substituents "R" have the same identifications as set out in the definitions of the compounds disclosed below.



In the approaches disclosed below, "Protocol A" is the synthetic approach up to formula (III), and "Protocol B" is the synthetic approach up to formula (V). It is noted that in each of these approaches, the compound produced by Protocol A is then in turn used as the starting material for the compound produced by Protocol B.

Compounds of formulas (III) and (V) or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as a GPR6 inverse agonists. The data developed herein supports the conclusion that GPR6 inverse agonists are of use for the treatment or prophylaxis of clinical obesity or

overweight disorders in mammals, including, but not limited to, human. Compounds of the formulas (III) and (V) may be administered by oral, sublingual, parenteral, rectal, topical administration or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

In addition to the neutral forms of compounds of formulas (III) and (V) by appropriate addition of an ionizable substituent, which does not alter the receptor specificity of the compound, physiologically acceptable salts of the compounds may also be formed and used as therapeutic agents. Different amounts of the compounds of formulas (III) and (V) will be required to achieve the desired biological effect. The amount will depend on factors such as the specific compound, the use for which it is intended, the means of administration, and the condition of the treated individual — all of these dosing parameters are within the level of one of ordinary skill in the medicinal arts. A typical dose may be expected to fall in the range of 0.001 to 200 mg per kilogram of body weight of the mammal. Unit doses may contain from 1 to 200 mg of the compounds of formula (III) or (V) and may be administered one or more times a day, individually or in multiples. In the case of the salt or solvate of a compound of formulas (III) and (V), the dose is based on the cation (for salts) or the unsolvated compound.

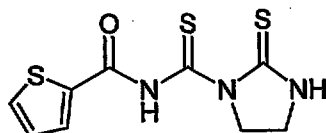
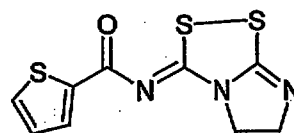
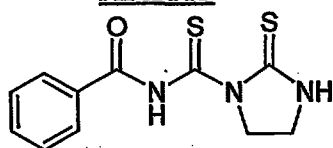
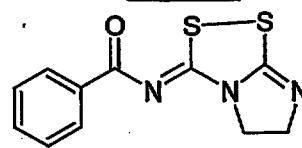
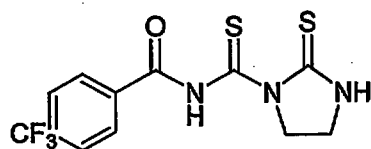
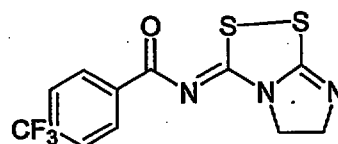
Compositions, including, but not limited to, pharmaceutical compositions, comprising at least one compound of formulas (III) and (V) and/or an acceptable salt or solvate thereof

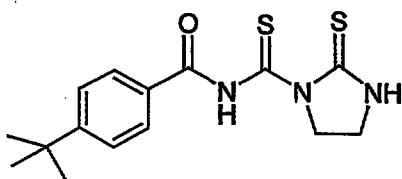
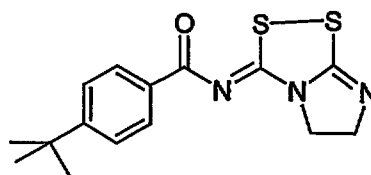
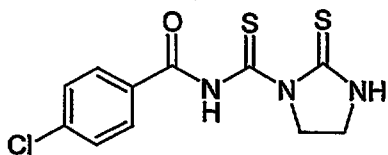
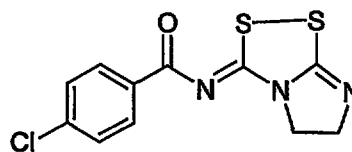
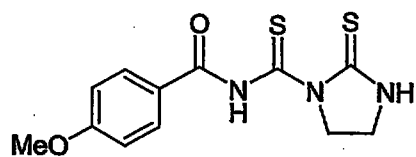
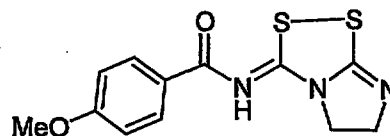
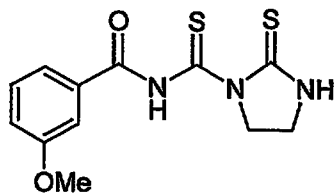
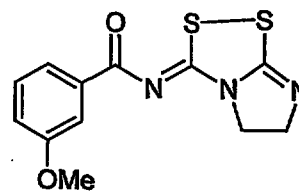
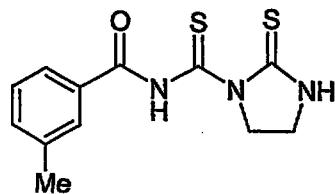
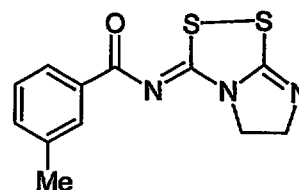
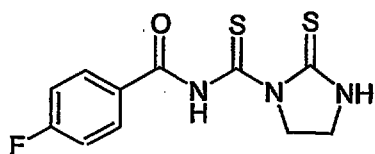
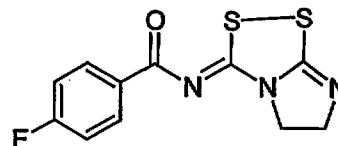
(e.g., a pharmaceutically acceptable salt or solvate) as an active ingredient combined with at least one carrier or excipient (e.g., pharmaceutical carrier or excipient). Pharmaceutical compositions may be used in the treatment of clinical conditions for which a GPR6 inverse agonist is indicated. At least one compound of formula (III) and (V) may be combined with the carrier in either solid or liquid form in a unit dose formulation. The pharmaceutical carrier must be compatible with the other ingredients in the composition and must be tolerated by the individual recipient. Other physiologically active ingredients may be incorporated into the pharmaceutical composition of the invention if desired, and if such ingredients are compatible with the other ingredients in the composition. Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

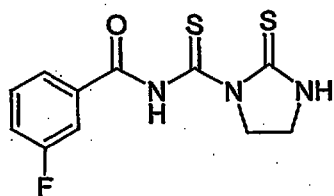
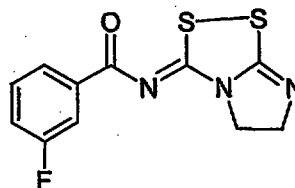
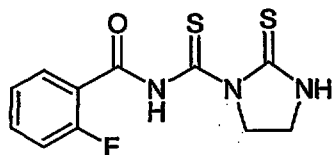
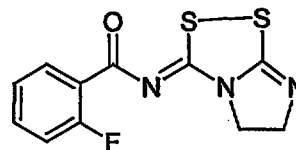
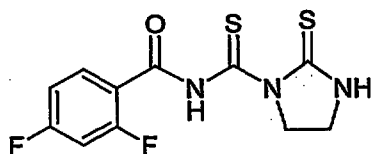
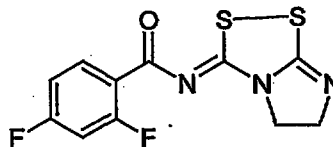
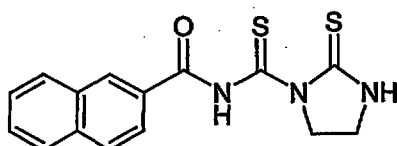
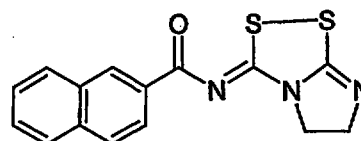
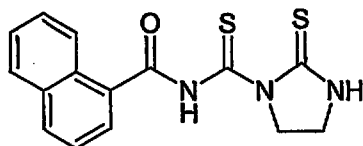
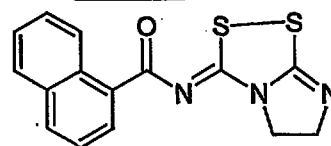
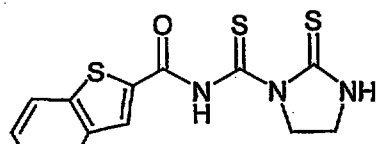
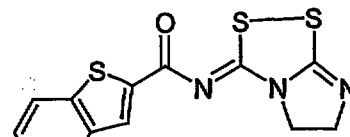
Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

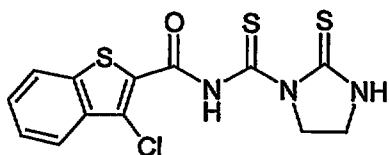
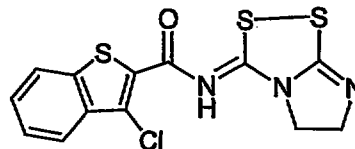
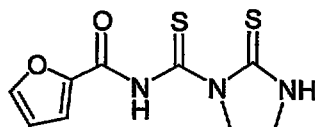
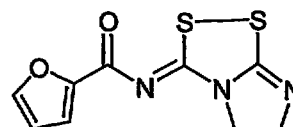
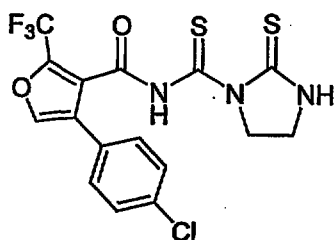
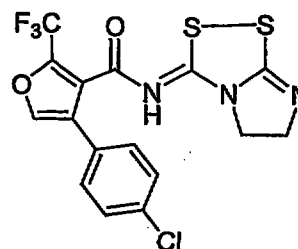
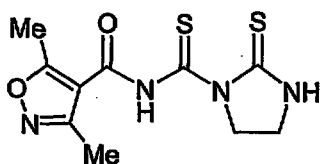
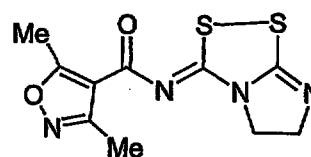
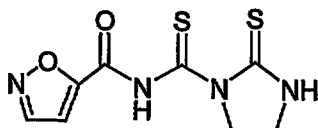
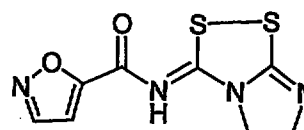
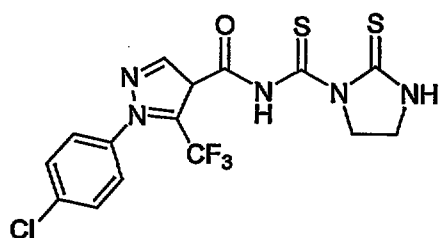
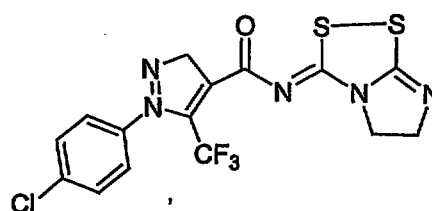
It is noted that when the GPR6 inverse agonists are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of GPR6 inverse agonists for the treatment of obesity in domestic animals (*e.g.*, cats and dogs), and GPR6 agonists in other domestic animals where no disease or disorder is evident (*e.g.*, food-oriented animals such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

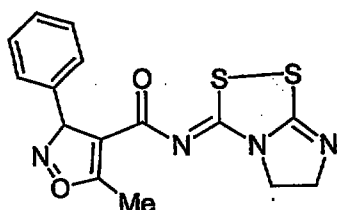
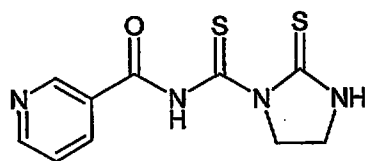
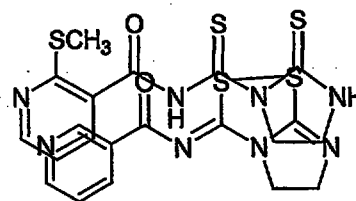
Below are structural representations of compounds that have been determined to exhibit similar GPR6 inverse agonist activity and selectivity as that of compound ARE112.

ARE111ARE112ARE113ARE114ARE115ARE116

ARE117.ARE118ARE119ARE120ARE121ARE122ARE123ARE124ARE125ARE126ARE127ARE128

ARE129ARE130ARE131ARE132ARE133ARE134ARE135ARE136ARE137ARE138ARE139ARE140

ARE141ARE142ARE143ARE144ARE145ARE146ARE147ARE148ARE149ARE150ARE151ARE152

ARE153ARE155ARE154ARE156**EXAMPLE 8B****PPREPARATION OF COMPOUNDS ARE111 – ARE156**

Mass spectra were recorded on a PE Sciex API 150 EX mass spectrometer linked to a Shimadzu dual pump (two LC8 pumps) HPLC using a CombiScreen C18 reverse phase column (50 mm x 4.6 mm i.d.). Gradient elution was over 5 minutes with 95% water containing 0.05% TFA/5% acetonitrile containing 0.35% TFA down to 100% acetonitrile at a flow rate of 3.5ml/min. Samples eluting from the HPLC were routinely monitored at 220nm using a Shimadzu SPD-10AVP detector unless otherwise stated. All reagents were purchased from commercial sources.

Preparation 1**Preparation and Analysis of**

ARE111 N-(2-thioxo-imidazolidine-1-carbothieryl)-thiophene-2-carboxamide and
ARE112 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-thiophen-2-carboxamide

The following synthetic protocols were used to generate each of the compounds below:

Protocol A:

To a freshly prepared solution of potassium thiocyanate (2.14g, 22mmol) in dry acetone (80ml), thiophene-2-carbonyl chloride (2.93g, 20mmol) was added dropwise at room temperature; the reaction mixture was then heated under a reflux for 15 min to give thiophene-2-carbonyl isothiocyanate *in situ* as a yellow suspension. The heating was stopped and 2-imidazolidinethione (2.04g, 20mmol) was added. The mixture was then heated under reflux for an additional 4 hours before being allowed to cool followed by stirring at room temperature overnight (15 hours). 50 ml of water was added and the mixture was further stirred at room temperature for a few minutes. The resulting precipitate was collected by filtration and washed with water, water/methanol (1:1) and methanol to give the compound ARE111 (2.865g, yield = 53%)

Mass spectrum: m/z (%): 272.0 (M+H, 100) Calculated for $C_9H_9N_3OS_3$ = 270.98

HPLC retention time: 2.97 min

Protocol B:

To a suspension of ARE111 (2g, 7.37mmol) in ethanol (30ml) was added concentrated hydrochloric acid (0.75ml) and 30% hydrogen peroxide (2ml). The reaction mixture was heated under reflux in an oil bath for two hours while the yellow suspension turned white. The resulting precipitate was collected by filtration and washed with ethanol to give the hydrochloride salt that was then suspended in ethanol (20ml) and treated with 28-30% ammonium hydroxide (1ml) to yield the free base. The reaction mixture was stirred at room temperature for 20 min then the resulting precipitate was collected by filtration, washed with ethanol and dried to give the compound ARE112 (1.304g, yield = 66%) as a yellowish solid.

MS (ES+): m/z (%): 270 (M+H, 100)

Mass spectrum: m/z (%): 270.0 (M+H, 100) Calculated for $C_9H_7N_3OS_3 = 268.98$

HPLC retention time: 2.36 min

Preparation 2

Preparation and Analysis of

ARE113 N-(2-thioxo-imidazolidine-1-carbothioyl)-benzamide and

ARE114 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-benzamide

The procedure of Protocol A above was followed, using benzoyl chloride instead of thiophene-2-carbonyl chloride, to yield ARE113 as a yellowish solid.

Mass spectrum: m/z (%): 266.0 (M+H, 100) Calculated for $C_{11}H_{11}N_3OS_2 = 265.02$

HPLC retention time: 3.29 min

The procedure of Protocol B above was followed, using ARE113 instead of ARE111, to yield ARE114 as a white solid.

Mass spectrum: m/z (%): 263.8 (M+H, 61) Calculated for $C_{11}H_9N_3OS_2 = 263.02$

HPLC retention time: 2.53 min

Preparation 3

Preparation and Analysis of

ARE115 N-(2-thioxo-imidazolidine-1-carbothioyl)-4-trifluoromethylbenzamide and

ARE116 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-4-trifluoromethylbenzamide

Protocol A was followed using 4-(trifluoromethyl)benzoyl chloride instead of thiophen-2-carbonyl chloride to yield ARE115 as a yellowish solid.

Mass spectrum: m/z (%): 173.0 (100), 334.2 (M+H, 83) Calculated for

$C_{12}H_{10}F_3N_3OS_2 = 333.01$

HPLC retention time: 3.69 min

Protocol B was followed using ARE115 instead of ARE111 to yield ARE116 as a white solid.

Mass spectrum: m/z (%): 332.0 (M+H, 100) Calculated for $C_{12}H_{12}F_3N_3OS_2$ = 331.01

HPLC retention time: 3.28 min

Preparation 4

Preparation and Analysis of

ARE117 N-(2-thioxo-imidazolidine-1-carbothioyl)-4-tert-butylbenzamide and
ARE118 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-4-tert-butylbenzamide

Protocol A was followed using 4-tert-butylbenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE117 as a yellowish solid.

Mass spectrum: m/z (%): 161.0 (100), 322.0 (M+H, 53) Calculated for $C_{15}H_{19}N_3OS_2$ = 321.45

HPLC retention time: 3.97 min

Protocol B was followed using ARE117 instead of ARE111 to yield compound ARE118 as a white solid.

Mass spectrum: m/z (%): 320.0 (M+H, 100) Calculated for $C_{15}H_{17}N_3OS_2$ = 319.45

HPLC retention time: 3.72 min

Preparation 5

Preparation and Analysis of

ARE119 N-(2-thioxo-imidazolidine-1-carbothioyl)-4-chlorobenzamide and
ARE120 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-4-chlorobenzamide

Protocol A was followed using 4-chlorobenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE119 as a yellowish solid.

Mass spectrum: m/z (%): 139.0 (100), 300.0 (M+H, 56) Calculated for $C_{11}H_{10}ClN_3OS_2$
= 298.98

HPLC retention time: 3.52 min

Protocol B was followed using ARE119 instead of ARE111 to yield compound ARE120 as a white solid.

Mass spectrum: m/z (%): 139.0 (100), 298.0 (M+H, 72) Calculated for $C_{11}H_8ClN_3OS_2$
= 296.98

HPLC retention time: 3.01 min

Preparation 6

Preparation and Analysis of

ARE121 N-(2-thioxo-imidazolidine-1-carbothioyl)-4-methoxybenzamide and
ARE122 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-4-methoxybenzamide

Protocol A was followed using 4-methoxybenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE121 as a yellowish solid.

Mass spectrum: m/z (%): 135.0 (100), 296.2 (M+H, 39) Calculated for $C_{12}H_{13}N_3O_2S_2$
= 295.03

HPLC retention time 3.37 min

Protocol B was followed using ARE121 instead of ARE111 to yield compound ARE122 as a white solid.

Mass spectrum: m/z (%): 294.0 (M+H, 100) Calculated for $C_{12}H_{11}N_3O_2S_2$ = 293.03

HPLC retention time: 2.89 min

Preparation 7

Preparation and Analysis of

ARE123 N-(2-thioxo-imidazolidine-1-carbothioyl)-3-methoxybenzamide and
ARE124 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-3-methoxybenzamide

Protocol A was followed using 3-methoxybenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE123 as a yellowish solid.

Mass spectrum: m/z (%): 135.2 (100), 296.2 (M+H, 53) Calculated for $C_{12}H_{13}N_3O_2S_2$
= 295.03

HPLC retention time: 3.20 min

Protocol B was followed using ARE123 instead of ARE111 to yield ARE124 as a white solid.

Mass spectrum: m/z (%): 294.0 (M+H, 100) Calculated for $C_{12}H_{11}N_3O_2S_2$ = 293.03

HPLC retention time: 2.94 min

Preparation 8

Preparation and Analysis of

ARE125 N-(2-thioxo-imidazolidine-1-carbothioyl)-3-methylbenzamide and
ARE126 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-3-methylbenzamide

Protocol A was followed using 3-methylbenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE125 as a yellowish solid.

Mass spectrum: m/z (%): 119.4 (100), 280.0 (M+H, 47) Calculated for $C_{12}H_{13}N_3OS_2$
= 279.03

HPLC retention time: 3.59 min

Protocol B was followed using ARE125 instead of ARE111 to yield compound ARE126 as a white solid.

Mass spectrum: m/z (%): 278.0 (M+H, 100) Calculated for $C_{12}H_{11}N_3OS_2$ = 277.03

HPLC retention time: 3.11 min

Preparation 9

Preparation and Analysis of

**ARE127 N-(2-thioxo-imidazolidine-1-carbothiyl)-4-fluorobenzamide and
ARE128 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-4-fluorobenzamide**

Protocol A was followed using 4-fluorobenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE127 as a yellowish solid.

Mass spectrum: m/z (%): 123.2 (100), 284.2 (M+H, 75) Calculated for $C_{11}H_{10}FN_3OS_2$ = 283.01

Protocol B was followed using ARE127 instead of ARE111 to compound ARE128 as a white solid.

Mass spectrum: m/z (%): 123.2 (100), 282.2 (M+H, 90) Calculated for $C_{11}H_8FN_3OS_2$ = 281.01

HPLC retention time: 2.68 min

Preparation 10

**Preparation and Analysis of
ARE129 N-(2-thioxo-imidazolidine-1-carbothiyl)-3-fluorobenzamide and
ARE130 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-3-fluorobenzamide**

Protocol A was followed using 3-fluorobenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE129 as a yellowish solid.

Mass spectrum: m/z (%): 123.2 (100), 284.3 (M+H, 61) Calculated for $C_{11}H_{10}FN_3OS_2$ = 283.01

HPLC retention time: 3.24 min

Protocol B was followed using ARE129 instead of ARE111 to yield compound ARE130 as a white solid.

Mass spectrum: m/z (%): 282.2 (M+H, 100) Calculated for $C_{11}H_8FN_3OS_2$ = 281.01

HPLC retention time: 2.97 min

Preparation 11

Preparation and Analysis of

ARE131 N-(2-thioxo-imidazolidine-1-carbothioyl)-2-fluorobenzamide and

ARE132 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-2-fluorobenzamide

Protocol A was followed using 2-fluorobenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE131 as a yellowish solid.

Mass spectrum: m/z (%): 123.2 (100), 284.0 (M+H, 67) Calculated for $C_{11}H_{10}FN_3OS_2$ = 283.01

HPLC retention time: 3.07 min

Protocol B was followed using ARE131 instead of ARE111 to yield compound ARE132 as a white solid.

Mass spectrum: m/z (%): 282.2 (M+H, 100) Calculated for $C_{11}H_8FN_3OS_2$ = 281.01

HPLC retention time: 2.72 min

Preparation 12

Preparation and Analysis of

ARE133 N-(2-thioxo-imidazolidine-1-carbothioyl)-2,4-difluorobenzamide and

ARE134 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-2,4-difluorobenzamide

Protocol A was followed using 2,4-difluorobenzoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE133 as a yellow solid.

Mass spectrum: m/z (%): 141.0 (100), 302.2 (M+H, 39) Calculated for $C_{11}H_9F_2N_3OS_2$ = 301.00

HPLC retention time: 3.23 min

Protocol B was followed using ARE133 instead of ARE111 to yield compound ARE134 as a white solid.

Mass spectrum: m/z (%): 300.0 (M+H, 100) Calculated for $C_{11}H_7F_2N_3OS_2$ = 299.00

HPLC retention time: 2.86 min

Preparation 13

Preparation and Analysis of

ARE135 N-(2-thioxo-imidazolidine-1-carbothiyl)-naphthyl-2-carboxamide and
ARE136 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-naphthyl-
carboxamide

Protocol A was followed using 2-naphthoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE135 as a yellowish solid.

Mass spectrum: m/z (%): 155.0(100), 316.0 (M+H, 56) Calculated for

$C_{15}H_{13}N_3OS_2 = 315.40$

HPLC retention time: 3.88 min

Protocol B was followed using ARE135 instead of ARE111 to yield compound ARE136 as a white solid.

Mass spectrum: m/z (%): 314.0 (M+H, 100) Calculated for $C_{15}H_{11}N_3OS_2 = 313.40$

HPLC retention time: 3.41 min

Preparation 14

Preparation and Analysis of

ARE137 N-(2-thioxo-imidazolidine-1-carbothiyl)- naphthyl-1-carboxamide and
ARE138 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)- naphthyl-1-
carboxamide

Protocol A was followed using 1-naphthoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE137 as a yellow solid.

Mass spectrum: m/z (%): 155.0 (100), 316.0 (M+H, 39) Calculated for

$C_{15}H_{13}N_3OS_2 = 315.40$

HPLC retention time: 3.80 min

Protocol B will be followed using ARE137 instead of ARE111 to yield ARE138 as a white solid.

Mass spectrum: m/z (%): 314.0 (M+H, 100) Calculated for $C_{15}H_{13}N_3OS_2 = 313.05$

HPLC retention time: 3.38 min

Preparation 15

Preparation and Analysis of

ARE139 N-(2-thioxo-imidazolidine-1-carbothiyl)-benzothiophen-2-carboxamide and
ARE140 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-benzothiophen-2-carboxamide

Protocol A was followed using benzo[b]thiophene-2-carbonyl chloride instead of thiophene-2-carbonyl chloride, to yield compound ARE139 as a yellowish solid.

Mass spectrum: m/z (%): 160.8 (100), 321.8 (M+H, 51) Calculated for

$C_{13}H_{11}N_3OS_3 = 320.99$

HPLC retention time: 3.92 min

Protocol B was followed using ARE139 instead of ARE111 to yield compound ARE140 as a white solid.

Mass spectrum: m/z (%): 320.0 (M+H, 100) Calculated for $C_{13}H_9N_3OS_3 = 318.99$

HPLC retention time: 3.47 min

Preparation 16

Preparation and Analysis of

ARE143 N-(2-thioxo-imidazolidine-1-carbothiyl)-furan-2-carboxamide and
ARE144 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-furan-2-carboxamide

Protocol A was followed using 2-furoyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE143 as a yellowish solid.

Mass spectrum: m/z (%): 256.0 (M+H, 100) Calculated for $C_9H_9N_3O_2S_2 = 255.00$

HPLC retention time: 2.86 min

Protocol B was followed using ARE143 instead of ARE111 to yield compound ARE144 as a white solid.

Mass spectrum: m/z (%): 254.2 (M+H, 100) Calculated for $C_9H_9N_3O_2S_2$ = 253.00

HPLC retention time: 2.13 min

Preparation 17

Preparation and Analysis of ARE148 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-2,5-dimethylisoxazole-4-carboxamide

Protocol A was followed using 2,5-dimethylisoxazole-4-carbonyl chloride instead of thiophene-2-carbonyl chloride to yield compound N-(2-thioxo-imidazolidine-1-carbothioyl)-2,5-dimethylisoxazole-4-carboxamide as a yellowish solid.

Protocol B was then followed using the above compound instead of ARE111 to yield compound ARE148 as a white solid.

Mass spectrum: m/z (%): 283.0 (M+H, 100) Calculated for $C_{10}H_{10}N_4O_2S_2$ = 282.02

HPLC retention time: 2.53 min

Preparation 18

Preparation and Analysis of ARE149 N-(2-thioxo-imidazolidine-1-carbothioyl)-isoxazole-3-carboxamide and ARE150 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-isoxazole-3-carboxamide

Protocol A was followed using isoxazole-3-carbonyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE149 as a yellowish solid.

Mass spectrum: m/z (%): 257.0 (M+H, 100) Calculated for $C_8H_8N_4O_2S_2$ = 255.99

HPLC retention time: 2.76 min

Protocol B was followed using ARE149 instead of ARE111 to yield compound ARE150 as a white solid.

Mass spectrum: m/z (%): 255.2 (M+H, 100) Calculated for $C_8H_6N_4O_2S_2$ = 253.99

HPLC retention time: 2.09 min

Preparation 19

Preparation and Analysis of

ARE151 N-(2-thioxo-imidazolidine-1-carbothioid)-2-(4-chlorophenyl)-3-(trifluoromethyl)pyrazole-4-carboxamide and

ARE152 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-2-(4-chlorophenyl)-3-(trifluoromethyl)pyrazole-4-carboxamide

Protocol A was followed using 2-(4-chlorophenyl)-3-(trifluoromethyl)pyrazole-4-carbonyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE151 as a yellowish solid.

Mass spectrum: m/z (%): 273.0 (100), 434.0 (M+H, 76) Calculated for $C_{15}H_{11}ClF_3N_4O_2S_2$ = 432.99

HPLC retention time: 4.25 min

Protocol B was followed using ARE151 instead of ARE111 to yield compound ARE152 as a white solid.

Mass spectrum: m/z (%): 431.8 (M+H, 100) Calculated for

$C_{15}H_9ClF_3N_5OS_2$ = 431.8

HPLC retention time: 3.77 min

Preparation 20

Preparation and Analysis of

ARE153 N-(2-thioxo-imidazolidine-1-carbothioid)-2-(4-chlorophenyl)-3-(trifluoromethyl)pyrazole-4-carboxamide

Protocol A was followed using 2-methyl-5-phenylisoxazole-4-carbonyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE153 as a yellowish solid.

Mass spectrum: m/z (%): 344.8 (100), (M+H, 100) Calculated for

$C_{15}H_{12}N_4O_2S_2 = 344.42$

HPLC retention time: 4.57 min

Preparation 21

Preparation and Analysis of ARE154 N-(2-thioxo-imidazolidine-1-carbothioyl)-pyridine-2-methylthio-3-carboxamide

Protocol A was followed using pyridine-2-methylthio-3-carbonyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE154 as a yellowish solid.

Mass spectrum: m/z (%): 152.2 (100), 313.2 (M+H, 100) Calculated for $C_{11}H_{12}N_4OS_3 =$

312.02

HPLC retention time: 3.31 min

Preparation 22

Preparation and Analysis of ARE155 N-(2-thioxo-imidazolidine-1-carbothioyl)-pyridine-3-carboxamide and ARE156 N-(5,6-dihydro-3H-imidazo[2,1-c]-1,2,4-dithiazol-3-ylidene)-pyridine-3-carboxamide

Protocol A was followed using pyridine-3-carbonyl chloride instead of thiophene-2-carbonyl chloride to yield compound ARE155 as a yellowish solid.

Mass spectrum: m/z (%): 165.0 (100), 267.0 (M+H, 50)

Calculated for $C_{10}H_{10}N_4OS_2 = 266.03$

HPLC retention time: 2.29 min

Protocol B was followed using ARE155 instead of ARE111 to yield compound ARE156 as a white solid.

Mass spectrum: m/z (%): 265.0 (M+H, 100)

Calculated for $C_{10}H_8N_4OS_2$ = 264.01

HPLC retention time: 1.87 min

Different embodiments of the invention will consist of different constitutively active receptors, expression systems, different assays, and different compounds. Those skilled in the art will understand which receptors to use with which expression systems and assay methods. All are considered within the scope of the teaching of this invention. In addition, those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. Indeed, with the assay systems disclosed above, as well as the relationship between the receptor GPR6 and feeding behavior, one of ordinary skill in the art is readily credited with the ability to directly identify small molecule inverse agonists, agonists and partial agonists to the receptor — for example, we note that the phrase “small molecule GPR6 inverse agonist” is not limited by the specific compounds disclosed herein.

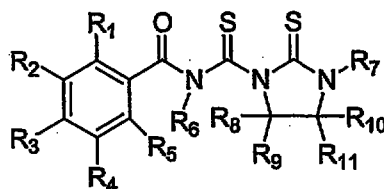
All patent documents, applications, and printed publications cited throughout this patent document, including provisional applications and regular patent applications, unless otherwise indicated, are incorporated herein in their entirety by reference. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

CLAIMS



What is claimed is:

1. A small molecule, GPR6 inverse agonist.
2. A method for modulating by inverse agonism the G protein-coupled receptor, GPR6, comprising the step of contacting GPR6 with a small molecule GPR6 inverse agonist.
3. The small molecule, GPR6 inverse agonist of claim 1 structurally represented as follows:



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN, $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;



R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$ wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl, and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position on said aryl, each said position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$,



COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇,
CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring, said aryl ring being substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N and S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN,

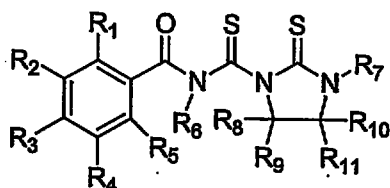


COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅,
 COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅,
 CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂;
 or

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

4. The method of claim 2 wherein the small molecule, GPR6 inverse agonist is structurally represented as follows:



wherein R¹, R², R³, R⁴, and R⁵ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴,
 NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹²,
 OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃,
 PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴,
 and



wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR^{13}R^{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$ wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl, and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position on said aryl, each said position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_6H_{11} , OC_7H_{13} , OC_8H_{17} , OC_9H_{19} , $OC_{10}H_{21}$, $OC_{11}H_{23}$, $OC_{12}H_{25}$, $OC_{13}H_{27}$, $OC_{14}H_{29}$, $OC_{15}H_{31}$, $OC_{16}H_{33}$, $OC_{17}H_{35}$, $OC_{18}H_{37}$, $OC_{19}H_{39}$, $OC_{20}H_{41}$, $OC_{21}H_{43}$, $OC_{22}H_{45}$, $OC_{23}H_{47}$, $OC_{24}H_{49}$, $OC_{25}H_{51}$, $OC_{26}H_{53}$, $OC_{27}H_{55}$, $OC_{28}H_{57}$, $OC_{29}H_{59}$, $OC_{30}H_{61}$, $OC_{31}H_{63}$, $OC_{32}H_{65}$, $OC_{33}H_{67}$, $OC_{34}H_{69}$, $OC_{35}H_{71}$, $OC_{36}H_{73}$, $OC_{37}H_{75}$, $OC_{38}H_{77}$, $OC_{39}H_{79}$, $OC_{40}H_{81}$, $OC_{41}H_{83}$, $OC_{42}H_{85}$, $OC_{43}H_{87}$, $OC_{44}H_{89}$, $OC_{45}H_{91}$, $OC_{46}H_{93}$, $OC_{47}H_{95}$, $OC_{48}H_{97}$, $OC_{49}H_{99}$, $OC_{50}H_{101}$, $OC_{51}H_{103}$, $OC_{52}H_{105}$, $OC_{53}H_{107}$, $OC_{54}H_{109}$, $OC_{55}H_{111}$, $OC_{56}H_{113}$, $OC_{57}H_{115}$, $OC_{58}H_{117}$, $OC_{59}H_{119}$, $OC_{60}H_{121}$, $OC_{61}H_{123}$, $OC_{62}H_{125}$, $OC_{63}H_{127}$, $OC_{64}H_{129}$, $OC_{65}H_{131}$, $OC_{66}H_{133}$, $OC_{67}H_{135}$, $OC_{68}H_{137}$, $OC_{69}H_{139}$, $OC_{70}H_{141}$, $OC_{71}H_{143}$, $OC_{72}H_{145}$, $OC_{73}H_{147}$, $OC_{74}H_{149}$, $OC_{75}H_{151}$, $OC_{76}H_{153}$, $OC_{77}H_{155}$, $OC_{78}H_{157}$, $OC_{79}H_{159}$, $OC_{80}H_{161}$, $OC_{81}H_{163}$, $OC_{82}H_{165}$, $OC_{83}H_{167}$, $OC_{84}H_{169}$, $OC_{85}H_{171}$, $OC_{86}H_{173}$, $OC_{87}H_{175}$, $OC_{88}H_{177}$, $OC_{89}H_{179}$, $OC_{90}H_{181}$, $OC_{91}H_{183}$, $OC_{92}H_{185}$, $OC_{93}H_{187}$, $OC_{94}H_{189}$, $OC_{95}H_{191}$, $OC_{96}H_{193}$, $OC_{97}H_{195}$, $OC_{98}H_{197}$, $OC_{99}H_{199}$, $OC_{100}H_{201}$, $OC_{101}H_{203}$, $OC_{102}H_{205}$, $OC_{103}H_{207}$, $OC_{104}H_{209}$, $OC_{105}H_{211}$, $OC_{106}H_{213}$, $OC_{107}H_{215}$, $OC_{108}H_{217}$, $OC_{109}H_{219}$, $OC_{110}H_{221}$, $OC_{111}H_{223}$, $OC_{112}H_{225}$, $OC_{113}H_{227}$, $OC_{114}H_{229}$, $OC_{115}H_{231}$, $OC_{116}H_{233}$, $OC_{117}H_{235}$, $OC_{118}H_{237}$, $OC_{119}H_{239}$, $OC_{120}H_{241}$, $OC_{121}H_{243}$, $OC_{122}H_{245}$, $OC_{123}H_{247}$, $OC_{124}H_{249}$, $OC_{125}H_{251}$, $OC_{126}H_{253}$, $OC_{127}H_{255}$, $OC_{128}H_{257}$, $OC_{129}H_{259}$, $OC_{130}H_{261}$, $OC_{131}H_{263}$, $OC_{132}H_{265}$, $OC_{133}H_{267}$, $OC_{134}H_{269}$, $OC_{135}H_{271}$, $OC_{136}H_{273}$, $OC_{137}H_{275}$, $OC_{138}H_{277}$, $OC_{139}H_{279}$, $OC_{140}H_{281}$, $OC_{141}H_{283}$, $OC_{142}H_{285}$, $OC_{143}H_{287}$, $OC_{144}H_{289}$, $OC_{145}H_{291}$, $OC_{146}H_{293}$, $OC_{147}H_{295}$, $OC_{148}H_{297}$, $OC_{149}H_{299}$, $OC_{150}H_{301}$, $OC_{151}H_{303}$, $OC_{152}H_{305}$, $OC_{153}H_{307}$, $OC_{154}H_{309}$, $OC_{155}H_{311}$, $OC_{156}H_{313}$, $OC_{157}H_{315}$, $OC_{158}H_{317}$, $OC_{159}H_{319}$, $OC_{160}H_{321}$, $OC_{161}H_{323}$, $OC_{162}H_{325}$, $OC_{163}H_{327}$, $OC_{164}H_{329}$, $OC_{165}H_{331}$, $OC_{166}H_{333}$, $OC_{167}H_{335}$, $OC_{168}H_{337}$, $OC_{169}H_{339}$, $OC_{170}H_{341}$, $OC_{171}H_{343}$, $OC_{172}H_{345}$, $OC_{173}H_{347}$, $OC_{174}H_{349}$, $OC_{175}H_{351}$, $OC_{176}H_{353}$, $OC_{177}H_{355}$, $OC_{178}H_{357}$, $OC_{179}H_{359}$, $OC_{180}H_{361}$, $OC_{181}H_{363}$, $OC_{182}H_{365}$, $OC_{183}H_{367}$, $OC_{184}H_{369}$, $OC_{185}H_{371}$, $OC_{186}H_{373}$, $OC_{187}H_{375}$, $OC_{188}H_{377}$, $OC_{189}H_{379}$, $OC_{190}H_{381}$, $OC_{191}H_{383}$, $OC_{192}H_{385}$, $OC_{193}H_{387}$, $OC_{194}H_{389}$, $OC_{195}H_{391}$, $OC_{196}H_{393}$, $OC_{197}H_{395}$, $OC_{198}H_{397}$, $OC_{199}H_{399}$, $OC_{200}H_{401}$, $OC_{201}H_{403}$, $OC_{202}H_{405}$, $OC_{203}H_{407}$, $OC_{204}H_{409}$, $OC_{205}H_{411}$, $OC_{206}H_{413}$, $OC_{207}H_{415}$, $OC_{208}H_{417}$, $OC_{209}H_{419}$, $OC_{210}H_{421}$, $OC_{211}H_{423}$, $OC_{212}H_{425}$, $OC_{213}H_{427}$, $OC_{214}H_{429}$, $OC_{215}H_{431}$, $OC_{216}H_{433}$, $OC_{217}H_{435}$, $OC_{218}H_{437}$, $OC_{219}H_{439}$, $OC_{220}H_{441}$, $OC_{221}H_{443}$, $OC_{222}H_{445}$, $OC_{223}H_{447}$, $OC_{224}H_{449}$, $OC_{225}H_{451}$, $OC_{226}H_{453}$, $OC_{227}H_{455}$, $OC_{228}H_{457}$, $OC_{229}H_{459}$, $OC_{230}H_{461}$, $OC_{231}H_{463}$, $OC_{232}H_{465}$, $OC_{233}H_{467}$, $OC_{234}H_{469}$, $OC_{235}H_{471}$, $OC_{236}H_{473}$, $OC_{237}H_{475}$, $OC_{238}H_{477}$, $OC_{239}H_{479}$, $OC_{240}H_{481}$, $OC_{241}H_{483}$, $OC_{242}H_{485}$, $OC_{243}H_{487}$, $OC_{244}H_{489}$, $OC_{245}H_{491}$, $OC_{246}H_{493}$, $OC_{247}H_{495}$, $OC_{248}H_{497}$, $OC_{249}H_{499}$, $OC_{250}H_{501}$, $OC_{251}H_{503}$, $OC_{252}H_{505}$, $OC_{253}H_{507}$, $OC_{254}H_{509}$, $OC_{255}H_{511}$, $OC_{256}H_{513}$, $OC_{257}H_{515}$, $OC_{258}H_{517}$, $OC_{259}H_{519}$, $OC_{260}H_{521}$, $OC_{261}H_{523}$, $OC_{262}H_{525}$, $OC_{263}H_{527}$, $OC_{264}H_{529}$, $OC_{265}H_{531}$, $OC_{266}H_{533}$, $OC_{267}H_{535}$, $OC_{268}H_{537}$, $OC_{269}H_{539}$, $OC_{270}H_{541}$, $OC_{271}H_{543}$, $OC_{272}H_{545}$, $OC_{273}H_{547}$, $OC_{274}H_{549}$, $OC_{275}H_{551}$, $OC_{276}H_{553}$, $OC_{277}H_{555}$, $OC_{278}H_{557}$, $OC_{279}H_{559}$, $OC_{280}H_{561}$, $OC_{281}H_{563}$, $OC_{282}H_{565}$, $OC_{283}H_{567}$, $OC_{284}H_{569}$, $OC_{285}H_{571}$, $OC_{286}H_{573}$, $OC_{287}H_{575}$, $OC_{288}H_{577}$, $OC_{289}H_{579}$, $OC_{290}H_{581}$, $OC_{291}H_{583}$, $OC_{292}H_{585}$, $OC_{293}H_{587}$, $OC_{294}H_{589}$, $OC_{295}H_{591}$, $OC_{296}H_{593}$, $OC_{297}H_{595}$, $OC_{298}H_{597}$, $OC_{299}H_{599}$, $OC_{300}H_{601}$, $OC_{301}H_{603}$, $OC_{302}H_{605}$, $OC_{303}H_{607}$, $OC_{304}H_{609}$, $OC_{305}H_{611}$, $OC_{306}H_{613}$, $OC_{307}H_{615}$, $OC_{308}H_{617}$, $OC_{309}H_{619}$, $OC_{310}H_{621}$, $OC_{311}H_{623}$, $OC_{312}H_{625}$, $OC_{313}H_{627}$, $OC_{314}H_{629}$, $OC_{315}H_{631}$, $OC_{316}H_{633}$, $OC_{317}H_{635}$, $OC_{318}H_{637}$, $OC_{319}H_{639}$, $OC_{320}H_{641}$, $OC_{321}H_{643}$, $OC_{322}H_{645}$, $OC_{323}H_{647}$, $OC_{324}H_{649}$, $OC_{325}H_{651}$, $OC_{326}H_{653}$, $OC_{327}H_{655}$, $OC_{328}H_{657}$, $OC_{329}H_{659}$, $OC_{330}H_{661}$, $OC_{331}H_{663}$, $OC_{332}H_{665}$, $OC_{333}H_{667}$, $OC_{334}H_{669}$, $OC_{335}H_{671}$, $OC_{336}H_{673}$, $OC_{337}H_{675}$, $OC_{338}H_{677}$, $OC_{339}H_{679}$, $OC_{340}H_{681}$, $OC_{341}H_{683}$, $OC_{342}H_{685}$, $OC_{343}H_{687}$, $OC_{344}H_{689}$, $OC_{345}H_{691}$, $OC_{346}H_{693}$, $OC_{347}H_{695}$, $OC_{348}H_{697}$, $OC_{349}H_{699}$, $OC_{350}H_{701}$, $OC_{351}H_{703}$, $OC_{352}H_{705}$, $OC_{353}H_{707}$, $OC_{354}H_{709}$, $OC_{355}H_{711}$, $OC_{356}H_{713}$, $OC_{357}H_{715}$, $OC_{358}H_{717}$, $OC_{359}H_{719}$, $OC_{360}H_{721}$, $OC_{361}H_{723}$, $OC_{362}H_{725}$, $OC_{363}H_{727}$, $OC_{364}H_{729}$, $OC_{365}H_{731}$, $OC_{366}H_{733}$, $OC_{367}H_{735}$, $OC_{368}H_{737}$, $OC_{369}H_{739}$, $OC_{370}H_{741}$, $OC_{371}H_{743}$, $OC_{372}H_{745}$, $OC_{373}H_{747}$, $OC_{374}H_{749}$, $OC_{375}H_{751}$, $OC_{376}H_{753}$, $OC_{377}H_{755}$, $OC_{378}H_{757}$, $OC_{379}H_{759}$, $OC_{380}H_{761}$, $OC_{381}H_{763}$, $OC_{382}H_{765}$, $OC_{383}H_{767}$, $OC_{384}H_{769}$, $OC_{385}H_{771}$, $OC_{386}H_{773}$, $OC_{387}H_{775}$, $OC_{388}H_{777}$, $OC_{389}H_{779}$, $OC_{390}H_{781}$, $OC_{391}H_{783}$, $OC_{392}H_{785}$, $OC_{393}H_{787}$, $OC_{394}H_{789}$, $OC_{395}H_{791}$, $OC_{396}H_{793}$, $OC_{397}H_{795}$, $OC_{398}H_{797}$, $OC_{399}H_{799}$, $OC_{400}H_{801}$, $OC_{401}H_{803}$, $OC_{402}H_{805}$, $OC_{403}H_{807}$, $OC_{404}H_{809}$, $OC_{405}H_{811}$, $OC_{406}H_{813}$, $OC_{407}H_{815}$, $OC_{408}H_{817}$, $OC_{409}H_{819}$, $OC_{410}H_{821}$, $OC_{411}H_{823}$, $OC_{412}H_{825}$, $OC_{413}H_{827}$, $OC_{414}H_{829}$, $OC_{415}H_{831}$, $OC_{416}H_{833}$, $OC_{417}H_{835}$, $OC_{418}H_{837}$, $OC_{419}H_{839}$, $OC_{420}H_{841}$, $OC_{421}H_{843}$, $OC_{422}H_{845}$, $OC_{423}H_{847}$, $OC_{424}H_{849}$, $OC_{425}H_{851}$, $OC_{426}H_{853}$, $OC_{427}H_{855}$, $OC_{428}H_{857}$, $OC_{429}H_{859}$, $OC_{430}H_{861}$, $OC_{431}H_{863}$, $OC_{432}H_{865}$, $OC_{433}H_{867}$, $OC_{434}H_{869}$, $OC_{435}H_{871}$, $OC_{436}H_{873}$, $OC_{437}H_{875}$, $OC_{438}H_{877}$, $OC_{439}H_{879}$, $OC_{440}H_{881}$, $OC_{441}H_{883}$, $OC_{442}H_{885}$, $OC_{443}H_{887}$, $OC_{444}H_{889}$, $OC_{445}H_{891}$, $OC_{446}H_{893}$, $OC_{447}H_{895}$, $OC_{448}H_{897}$, $OC_{449}H_{899}$, $OC_{450}H_{901}$, $OC_{451}H_{903}$, $OC_{452}H_{905}$, $OC_{453}H_{907}$, $OC_{454}H_{909}$, $OC_{455}H_{911}$, $OC_{456}H_{913}$, $OC_{457}H_{915}$, $OC_{458}H_{917}$, $OC_{459}H_{919}$, $OC_{460}H_{921}$, $OC_{461}H_{923}$, $OC_{462}H_{925}$, $OC_{463}H_{927}$, $OC_{464}H_{929}$, $OC_{465}H_{931}$, $OC_{466}H_{933}$, $OC_{467}H_{935}$, $OC_{468}H_{937}$, $OC_{469}H_{939}$, $OC_{470}H_{941}$, $OC_{471}H_{943}$, $OC_{472}H_{945}$, $OC_{473}H_{947}$, $OC_{474}H_{949}$, $OC_{475}H_{951}$, $OC_{476}H_{953}$, $OC_{477}H_{955}$, $OC_{478}H_{957}$, $OC_{479}H_{959}$, $OC_{480}H_{961}$, $OC_{481}H_{963}$, $OC_{482}H_{965}$, $OC_{483}H_{967}$, $OC_{484}H_{969}$, $OC_{485}H_{971}$, $OC_{486}H_{973}$, $OC_{487}H_{975}$, $OC_{488}H_{977}$, $OC_{489}H_{979}$, $OC_{490}H_{981}$, $OC_{491}H_{983}$, $OC_{492}H_{985}$, $OC_{493}H_{987}$, $OC_{494}H_{989}$, $OC_{495}H_{991}$, $OC_{496}H_{993}$, $OC_{497}H_{995}$, $OC_{498}H_{997}$, $OC_{499}H_{999}$, $OC_{500}H_{1001}$, $OC_{501}H_{1003}$, $OC_{502}H_{1005}$, $OC_{503}H_{1007}$, $OC_{504}H_{1009}$, $OC_{505}H_{1011}$, $OC_{506}H_{1013}$, $OC_{507}H_{1015}$, $OC_{508}H_{1017}$, $OC_{509}H_{1019}$, $OC_{510}H_{1021}$, $OC_{511}H_{1023}$, $OC_{512}H_{1025}$, $OC_{513}H_{1027}$, $OC_{514}H_{1029}$, $OC_{515}H_{1031}$, $OC_{516}H_{1033}$, $OC_{517}H_{1035}$, $OC_{518}H_{1037}$, $OC_{519}H_{1039}$, $OC_{520}H_{1041}$, $OC_{521}H_{1043}$, $OC_{522}H_{1045}$, $OC_{523}H_{1047}$, $OC_{524}H_{1049}$, $OC_{525}H_{1051}$, $OC_{526}H_{1053}$, $OC_{527}H_{1055}$, $OC_{528}H_{1057}$, $OC_{529}H_{1059}$, $OC_{530}H_{1061}$, $OC_{531}H_{1063}$, $OC_{532}H_{1065}$, $OC_{533}H_{1067}$, $OC_{534}H_{1069}$, $OC_{535}H_{1071}$, $OC_{536}H_{1073}$, $OC_{537}H_{1075}$, $OC_{538}H_{1077}$, $OC_{539}H_{1079}$, $OC_{540}H_{1081}$, $OC_{541}H_{1083}$, $OC_{542}H_{1085}$, $OC_{543}H_{1087}$, $OC_{544}H_{1089}$, $OC_{545}H_{1091}$, $OC_{546}H_{1093}$, $OC_{547}H_{1095}$, $OC_{548}H_{1097}$, $OC_{549}H_{1099}$, $OC_{550}H_{1101}$, $OC_{551}H_{1103}$, $OC_{552}H_{1105}$, $OC_{553}H_{1107}$, $OC_{554}H_{1109}$, $OC_{555}H_{1111}$, $OC_{556}H_{1113}$, $OC_{557}H_{1115}$, $OC_{558}H_{1117}$, $OC_{559}H_{1119}$, $OC_{560}H_{1121}$, $OC_{561}H_{1123}$, $OC_{562}H_{1125}$, $OC_{563}H_{1127}$, $OC_{564}H_{1129}$, $OC_{565}H_{1131}$, $OC_{566}H_{1133}$, $OC_{567}H_{1135}$, $OC_{568}H_{1137}$, $OC_{569}H_{1139}$, $OC_{570}H_{1141}$, $OC_{571}H_{1143}$, $OC_{572}H_{1145}$, $OC_{573}H_{1147}$, $OC_{574}H_{1149}$, $OC_{575}H_{1151}$, $OC_{576}H_{1153}$, $OC_{577}H_{1155}$, $OC_{578}H_{1157}$, $OC_{579}H_{1159}$, $OC_{580}H_{1161}$, $OC_{581}H_{1163}$, $OC_{582}H_{1165}$, $OC_{583}H_{1167}$, $OC_{584}H_{1169}$, $OC_{585}H_{1171}$, $OC_{586}H_{1173}$, $OC_{587}H_{1175}$, $OC_{588}H_{1177}$, $OC_{589}H_{1179}$, $OC_{590}H_{1181}$, $OC_{591}H_{1183}$, $OC_{592}H_{1185}$, $OC_{593}H_{1187}$, $OC_{594}H_{1189}$, $OC_{595}H_{1191}$, $OC_{596}H_{1193}$, $OC_{597}H_{1195}$, $OC_{598}H_{1197}$, $OC_{599}H_{1199}$, $OC_{600}H_{1201}$, $OC_{601}H_{1203}$, $OC_{602}H_{1205}$, $OC_{603}H_{1207}$, $OC_{604}H_{1209}$, $OC_{605}H_{1211}$, $OC_{606}H_{1213}$, $OC_{607}H_{1215}$, $OC_{608}H_{1217}$, $OC_{609}H_{1219}$, $OC_{610}H_{1221}$, $OC_{611}H_{1223}$, $OC_{612}H_{1225}$, $OC_{613}H_{1227}$, $OC_{614}H_{1229}$, $OC_{615}H_{1231}$, $OC_{616}H_{1233}$, $OC_{617}H_{1235}$, $OC_{618}H_{1237}$, $OC_{619}H_{1239}$, $OC_{620}H_{1241}$, $OC_{621}H_{1243}$, $OC_{622}H_{1245}$, $OC_{623}H_{1247}$, $OC_{624}H_{1249}$, $OC_{625}H_{1251}$, $OC_{626}H_{1253}$, $OC_{627}H_{1255}$, $OC_{628}H_{1257}$, $OC_{629}H_{1259}$, $OC_{630}H_{1261}$, $OC_{631}H_{1263}$, $OC_{632}H_{1265}$, $OC_{633}H_{1267}$, $OC_{634}H_{1269}$, $OC_{635}H_{1271}$, $OC_{636}H_{1273}$, $OC_{637}H_{1275}$, $OC_{638}H_{1277}$, $OC_{639}H_{1279}$, $OC_{640}H_{1281}$, $OC_{641}H_{1283}$, $OC_{642}H_{1285}$, $OC_{643}H_{1287}$, $OC_{644}H_{1289}$, $OC_{645}H_{1291}$, $OC_{646}H_{1293}$, $OC_{647}H_{1295}$, $OC_{648}H_{1297}$, $OC_{649}H_{1299}$,



OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring, said aryl ring being substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N and S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃,

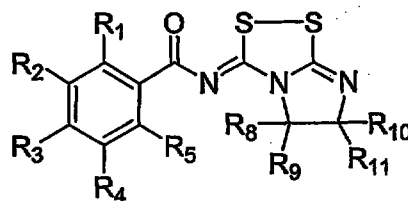
OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂;

or

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

5. The small molecule, GPR6 inverse agonist of claim 1 structurally represented as follows:



wherein R^1, R^2, R^3, R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN, $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1, R^2, R^3, R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure;

R^8, R^9, R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR^{13}R^{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$ wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:



F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ may form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:



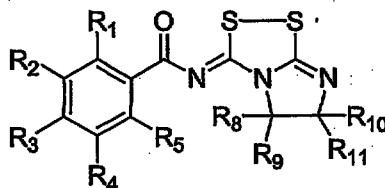
F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.



6. The method of claim 2 wherein the GPR6 inverse agonist is structurally represented as follows:



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN, $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;



R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$ wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$,



$\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; or

R^{13} and R^{14} may form part of a 5, 6 or 7 membered saturated cyclic structure or 5,6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

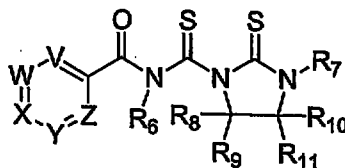
F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , NHCH_3 , $\text{N}(\text{CH}_3)_2$, NHC_2H_5 , $\text{N}(\text{C}_2\text{H}_5)_2$, NHC_3H_7 , $\text{N}(\text{C}_3\text{H}_7)_2$, NHC_4H_9 , $\text{N}(\text{C}_4\text{H}_9)_2$, NHCOH , NHCOCH_3 , NHCOC_2H_5 , NHCOC_3H_7 , NHCOC_4H_9 , NHSO_2CH_3 , $\text{NHSO}_2\text{C}_2\text{H}_5$, $\text{NHSO}_2\text{C}_3\text{H}_7$, $\text{NHSO}_2\text{C}_4\text{H}_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , OCOCH_3 , OCOC_2H_5 , OCOC_3H_7 , OCOC_4H_9 , OSO_2CH_3 , $\text{OSO}_2\text{C}_2\text{H}_5$, $\text{OSO}_2\text{C}_3\text{H}_7$, $\text{OSO}_2\text{C}_4\text{H}_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , SCOCH_3 , SCOC_2H_5 , SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$, $\text{SO}_3\text{C}_4\text{H}_9$, SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$, $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN , COOCH_3 , COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 , COSC_3H_7 , COSC_4H_9 , CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 , $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 , $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$,
and



wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl;

7. The small molecule, GPR6 inverse agonist of claim 1 structurally represented as follows:



wherein at least one of V, W, X, Y and Z is selected from N and each of V, W, X, Y, and Z that is/are not N are independently selected from CR^1 , CR^2 , CR^3 , CR^4 , and CR^5 , with the proviso that at least two of V, W, X, Y and Z are other than N;

R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN, $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and



wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 ,



SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇,

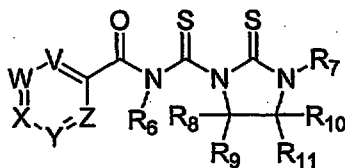


SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

8. The method of claim 2 wherein the small molecule, GPR6 inverse agonist is structurally represented as follows:



wherein at least one of V, W, X, Y and Z is selected from N and each of V, W, X, Y, and Z that is/are not N are independently selected from CR¹, CR², CR³, CR⁴, and CR⁵, with the proviso that at least two of V, W, X, Y and Z are other than N;

R¹, R², R³, R⁴, and R⁵ are each independently selected from the following:

H, F, Cl, Br, I, R¹², CF₃, CF₂R¹², CF₂CF₂, CCl₃, CCl₂R¹², CCl₂CCl₂R¹², NR¹³R¹⁴, NR¹⁵COR¹², NR¹⁵SO₂R¹², OR¹², OCF₃, OCF₂R¹², OCF₂CF₂R¹², OCOR¹², OSO₂R¹², OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R¹² is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, (CH₂)_nNR₁₃R₁₄, (CH₂)_mSO₃H, and (CH₂)_mCO₂H, wherein n is 2 through 6 and m is 1 through 6;



R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_5H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or



R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5,6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$,
and

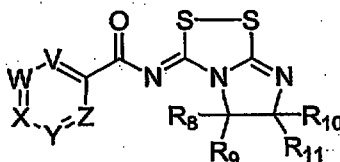
wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$,



$\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{SCH}_2\text{S}$, $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

9. The small molecule, GPR6 inverse agonist of claim 1, structurally represented as follows:



wherein at least one of V, W, X, Y and Z is selected from N and each of V, W, X, Y, and Z that is/are not N are independently selected from CR^1 , CR^2 , CR^3 , CR^4 , and CR^5 , with the proviso that at least two of V, W, X, Y and Z are other than N;

R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , $\text{CCl}_2\text{R}^{12}$, $\text{CCl}_2\text{CCl}_2\text{R}^{12}$, $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{15}\text{COR}^{12}$, $\text{NR}^{15}\text{SO}_2\text{R}^{12}$, OR^{12} , OCF_3 , $\text{OCF}_2\text{R}^{12}$, $\text{OCF}_2\text{CF}_2\text{R}^{12}$, OCOR^{12} , $\text{OSO}_2\text{R}^{12}$, $\text{OPO}(\text{OR}^{12})_2$, SR^{12} , SCF_3 , $\text{SCF}_2\text{R}^{12}$, $\text{SCF}_2\text{CF}_2\text{R}^{12}$, SCOR^{12} , SO_3R^{12} , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{PO}(\text{OR}^{12})_3$, $\text{PO}(\text{OR}^{12})_2\text{R}^{12}$, NO_2 , CN, $\text{CNR}^{15}(\text{NR}^{13}\text{R}^{14})$, $\text{CNR}^{15}(\text{SR}^{12})$, COOR^{12} , COSR^{12} , $\text{CONR}^{13}\text{R}^{14}$, and



wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 ,



* C L H S *

SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃,

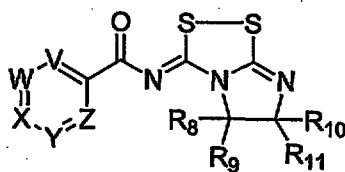


SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

10. The method of claim 2 wherein the small molecule, GPR6 inverse agonist is structurally represented as follows:



wherein at least one of V, W, X, Y and Z is selected from N and each of V, W, X, Y, and Z that is/are not N are independently selected from CR¹, CR², CR³, CR⁴, and CR⁵, with the proviso that at least two of V, W, X, Y and Z are other than N;



R^1, R^2, R^3, R^4 , and R^5 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN, $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1, R^2, R^3, R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure;

R^8, R^9, R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR^{13}R^{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:



F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:



F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

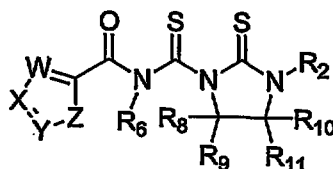
wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

11. The small molecule, GPR6 inverse agonist of claim 1 structurally represented as follows:



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wherein Z is selected from NR^4 , O and S;

W, X, or Y are independently selected from N, CR^1 , CR^2 , and CR^3 , with the proviso that when Z is O and Y is N, then W is CR^1 and X is CR^2 ;

R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , $\text{CCl}_2\text{R}^{12}$, $\text{CCl}_2\text{CCl}_2\text{R}^{12}$, $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{15}\text{COR}^{12}$, $\text{NR}^{15}\text{SO}_2\text{R}^{12}$, OR^{12} , OCF_3 , $\text{OCF}_2\text{R}^{12}$, $\text{OCF}_2\text{CF}_2\text{R}^{12}$, OCOR^{12} , $\text{OSO}_2\text{R}^{12}$, $\text{OPO}(\text{OR}^{12})_2$, SR^{12} , SCF_3 , $\text{SCF}_2\text{R}^{12}$, $\text{SCF}_2\text{CF}_2\text{R}^{12}$, SCOR^{12} , SO_3R^{12} , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{PO}(\text{OR}^{12})_3$, $\text{PO}(\text{OR}^{12})_2\text{R}^{12}$, NO_2 , CN, $\text{CNR}^{15}(\text{NR}^{13}\text{R}^{14})$, $\text{CNR}^{15}(\text{SR}^{12})$, COOR^{12} , COSR^{12} , $\text{CONR}^{13}\text{R}^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , and $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure;

R^4 is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl



R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or



R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5,6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

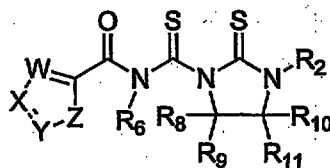
F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_5H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

12. The method of claim 2 wherein said small molecule, GPR6 inverse agonist is structurally represented as follows:





wherein Z is selected from NR^4 , O and S;

W, X, or Y are independently selected from N, CR^1 , CR^2 , and CR^3 , with the proviso that when Z is O and Y is N, then W is CR^1 and X is CR^2 ;

R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , $\text{CCl}_2\text{R}^{12}$, $\text{CCl}_2\text{CCl}_2\text{R}^{12}$, $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{15}\text{COR}^{12}$, $\text{NR}^{15}\text{SO}_2\text{R}^{12}$, OR^{12} , OCF_3 , $\text{OCF}_2\text{R}^{12}$, $\text{OCF}_2\text{CF}_2\text{R}^{12}$, OCOR^{12} , $\text{OSO}_2\text{R}^{12}$, $\text{OPO}(\text{OR}^{12})_2$, SR^{12} , SCF_3 , $\text{SCF}_2\text{R}^{12}$, $\text{SCF}_2\text{CF}_2\text{R}^{12}$, SCOR^{12} , SO_3R^{12} , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{PO}(\text{OR}^{12})_3$, $\text{PO}(\text{OR}^{12})_2\text{R}^{12}$, NO_2 , CN, $\text{CNR}^{15}(\text{NR}^{13}\text{R}^{14})$, $\text{CNR}^{15}(\text{SR}^{12})$, COOR^{12} , COSR^{12} , $\text{CONR}^{13}\text{R}^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , and $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure;

R^4 is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl



R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl and CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or



* C L M S *

R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

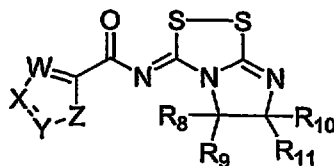
F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$,
and

wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , and OCH_2CH_2O to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

13. The small molecule, GPR6 inverse agonist of claim 1 structurally represented as follows:





wherein Z is selected from NR^4 , O and S;

W, X, or Y are independently selected from N, CR^1 , CR^2 , and CR^3 , with the proviso that when Z is O and Y is N, then W is CR^1 and X is CR^2 ;

R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , $\text{CCl}_2\text{R}^{12}$, $\text{CCl}_2\text{CCl}_2\text{R}^{12}$, $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{15}\text{COR}^{12}$, $\text{NR}^{15}\text{SO}_2\text{R}^{12}$, OR^{12} , OCF_3 , $\text{OCF}_2\text{R}^{12}$, $\text{OCF}_2\text{CF}_2\text{R}^{12}$, OCOR^{12} , $\text{OSO}_2\text{R}^{12}$, $\text{OPO}(\text{OR}^{12})_2$, SR^{12} , SCF_3 , $\text{SCF}_2\text{R}^{12}$, $\text{SCF}_2\text{CF}_2\text{R}^{12}$, SCOR^{12} , SO_3R^{12} , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{PO}(\text{OR}^{12})_3$, $\text{PO}(\text{OR}^{12})_2\text{R}^{12}$, NO_2 , CN, $\text{CNR}^{15}(\text{NR}^{13}\text{R}^{14})$, $\text{CNR}^{15}(\text{SR}^{12})$, COOR^{12} , COSR^{12} , $\text{CONR}^{13}\text{R}^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , and $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure;

R^4 is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl



R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, $(CH_2)_mCO_2H$ wherein n is 2 through 6 or m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or

R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up



* C L H S *

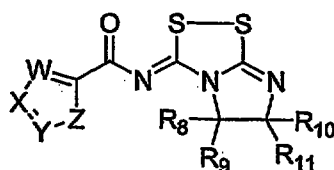
to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

14. The method of claim 2 wherein the small molecule, GPR6 inverse agonist is structurally represented as follows:



wherein Z is selected from NR^4 , O and S;

W, X, or Y are independently selected from N, CR^1 , CR^2 , and CR^3 , with the proviso that when Z is O and Y is N, then W is CR^1 and X is CR^2 ;

R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , $\text{CCl}_2\text{R}^{12}$, $\text{CCl}_2\text{CCl}_2\text{R}^{12}$, $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{15}\text{COR}^{12}$, $\text{NR}^{15}\text{SO}_2\text{R}^{12}$, OR^{12} , OCF_3 , $\text{OCF}_2\text{R}^{12}$, $\text{OCF}_2\text{CF}_2\text{R}^{12}$, OCOR^{12} , $\text{OSO}_2\text{R}^{12}$, $\text{OPO}(\text{OR}^{12})_2$, SR^{12} , SCF_3 , $\text{SCF}_2\text{R}^{12}$, $\text{SCF}_2\text{CF}_2\text{R}^{12}$, SCOR^{12} , SO_3R^{12} , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{PO}(\text{OR}^{12})_3$, $\text{PO}(\text{OR}^{12})_2\text{R}^{12}$, NO_2 , CN, $\text{CNR}^{15}(\text{NR}^{13}\text{R}^{14})$, $\text{CNR}^{15}(\text{SR}^{12})$, COOR^{12} , COSR^{12} , $\text{CONR}^{13}\text{R}^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , and $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure;

R^4 is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(\text{CH}_2)_n\text{NR}_{13}\text{R}_{14}$, $(\text{CH}_2)_m\text{SO}_3\text{H}$, $(\text{CH}_2)_m\text{CO}_2\text{H}$ wherein n is 2 through 6 or m is 1 through 6;



R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or

R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 ,

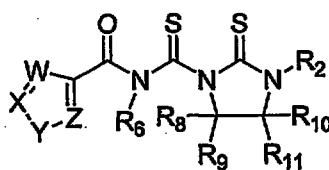


OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

R¹⁵ is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, and C₂₋₈ alkenyl.

15. The small molecule, GPR6 inverse agonist of claim 1 structurally represented as follows:



wherein Y is selected from NR⁴, O or S;

W, X, or Z are each independently selected from N or CR¹, CR², or CR³, with the proviso that when Y is O and Z is N, then W is CR¹ and X is CR²;



R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN , $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure;

R^4 is H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;



R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$,



$\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; or

R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

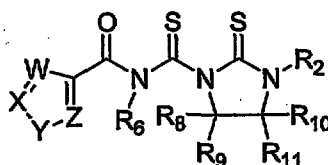
F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , NHCH_3 , $\text{N}(\text{CH}_3)_2$, NHC_2H_5 , $\text{N}(\text{C}_2\text{H}_5)_2$, NHC_3H_7 , $\text{N}(\text{C}_3\text{H}_7)_2$, NHC_4H_9 , $\text{N}(\text{C}_4\text{H}_9)_2$, NHCOH , NHCOCH_3 , NHCOC_2H_5 , NHCOC_3H_7 , NHCOC_4H_9 , NHSO_2CH_3 , $\text{NHSO}_2\text{C}_2\text{H}_5$, $\text{NHSO}_2\text{C}_3\text{H}_7$, $\text{NHSO}_2\text{C}_4\text{H}_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , OCOCH_3 , OCOC_2H_5 , OCOC_3H_7 , OCOC_4H_9 , OSO_2CH_3 , $\text{OSO}_2\text{C}_2\text{H}_5$, $\text{OSO}_2\text{C}_3\text{H}_7$, $\text{OSO}_2\text{C}_4\text{H}_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , SCOCH_3 , SCOC_2H_5 , SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$, $\text{SO}_3\text{C}_4\text{H}_9$, SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$, $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN , COOCH_3 , COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 , COSC_3H_7 , COSC_4H_9 , CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 , $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 , $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$, and



wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

16. The method of claim 2 wherein the small molecule, GPR6 inverse agonist is structurally represented as follows:



wherein Y is selected from NR^4 , O or S;

W, X, or Z are each independently selected from N or CR^1 , CR^2 , or CR^3 , with the proviso that when Y is O and Z is N, then W is CR^1 and X is CR^2 ;

R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} ,



OPO(OR¹²)₂, SR¹², SCF₃, SCF₂R¹², SCF₂CF₂R¹², SCOR¹², SO₃R¹², SO₂NR¹³R¹⁴, PO(OR¹²)₃, PO(OR¹²)₂R¹², NO₂, CN, CNR¹⁵(NR¹³R¹⁴), CNR¹⁵(SR¹²), COOR¹², COSR¹², CONR¹³R¹⁴, and

wherein any two adjacent positions of R¹, R², R³, R⁴, and R⁵ can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R⁴ is H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, COR⁵, CSR⁵, and SO₂R⁵;

R⁵, R⁶ and R⁷ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R⁶ and R⁷ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl

R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl and alkylaryl;

R¹² is selected from H, C₁₋₈ straight chain alkyl, branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl or cycloalkylalkyl, C₂₋₈ alkenyl, aryl, alkylaryl, (CH₂)_nNR¹³R¹⁴, (CH₂)_mSO₃H, and (CH₂)_mCO₂H, wherein n is 2 through 6 and m is 1 through 6;



R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, $CH_2CH_2SCH_2S$, SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; or



R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3 , $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3 , $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH_2 , SO_2NHCH_3 , $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2 , CN , $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

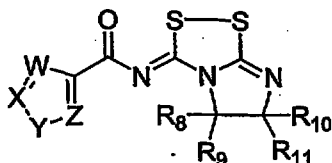
wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$,



$\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , SCH_2S , $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; and

R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

17. The small molecule, GPR6 inverse agonist of claim 1 structurally represented as follows:



wherein Y is selected from NR^4 , O or S;

W, X, or Z are each independently selected from N or CR^1 , CR^2 , or CR^3 , with the proviso that when Y is O and Z is N, then W is CR^1 and X is CR^2 ;

R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , $\text{CCl}_2\text{R}^{12}$, $\text{CCl}_2\text{CCl}_2\text{R}^{12}$, $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{15}\text{COR}^{12}$, $\text{NR}^{15}\text{SO}_2\text{R}^{12}$, OR^{12} , OCF_3 , $\text{OCF}_2\text{R}^{12}$, $\text{OCF}_2\text{CF}_2\text{R}^{12}$, OCOR^{12} , $\text{OSO}_2\text{R}^{12}$, $\text{OPO}(\text{OR}^{12})_2$, SR^{12} , SCF_3 , $\text{SCF}_2\text{R}^{12}$, $\text{SCF}_2\text{CF}_2\text{R}^{12}$, SCOR^{12} , SO_3R^{12} , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{PO}(\text{OR}^{12})_3$, $\text{PO}(\text{OR}^{12})_2\text{R}^{12}$, NO_2 , CN, $\text{CNR}^{15}(\text{NR}^{13}\text{R}^{14})$, $\text{CNR}^{15}(\text{SR}^{12})$, COOR^{12} , COSR^{12} , $\text{CONR}^{13}\text{R}^{14}$, and



wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure;

R^4 is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein



* C L H S *

each said aryl group or said aryl portion of said CH_2aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , NHCH_3 , $\text{N}(\text{CH}_3)_2$, NHC_2H_5 , $\text{N}(\text{C}_2\text{H}_5)_2$, NHC_3H_7 , $\text{N}(\text{C}_3\text{H}_7)_2$, NHC_4H_9 , $\text{N}(\text{C}_4\text{H}_9)_2$, NHCOH , NHCOCH_3 , NHCOC_2H_5 , NHCOC_3H_7 , NHCOC_4H_9 , NHSO_2CH_3 , $\text{NHSO}_2\text{C}_2\text{H}_5$, $\text{NHSO}_2\text{C}_3\text{H}_7$, $\text{NHSO}_2\text{C}_4\text{H}_9$, OH , OCH_3 , OC_2H_5 , OC_3H_7 , OC_4H_7 , OC_4H_9 , OC_5H_9 , OC_5H_{11} , OC_6H_{11} , OC_6H_{13} , OCF_3 , OCOCH_3 , OCOC_2H_5 , OCOC_3H_7 , OCOC_4H_9 , OSO_2CH_3 , $\text{OSO}_2\text{C}_2\text{H}_5$, $\text{OSO}_2\text{C}_3\text{H}_7$, $\text{OSO}_2\text{C}_4\text{H}_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_7 , SC_4H_9 , SC_5H_9 , SC_5H_{11} , SC_6H_{11} , SC_6H_{13} , SCF_3 , SCOCH_3 , SCOC_2H_5 , SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$, $\text{SO}_3\text{C}_4\text{H}_9$, SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$, $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN , COOCH_3 , COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 , COSC_3H_7 , COSC_4H_9 , CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 , $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 , $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$, and

wherein when R^{13} and/or R^{14} contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{SCH}_2\text{S}$, $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , or $\text{OCH}_2\text{CH}_2\text{O}$ to form a bi-cyclic structure; or

R^{13} and R^{14} form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each



said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

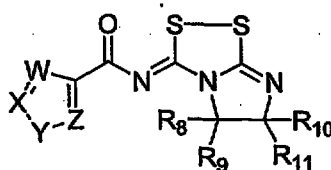
F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂,
and

wherein when R¹³ and R¹⁴ form an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂, SCH₂S, SCH₂CH₂S, OCH₂O, and OCH₂CH₂O to form a bi-cyclic structure; and



R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

18. The method of claim 2 wherein the small molecule, GPR6 inverse agonist is structurally represented as follows:



wherein Y is selected from NR^4 , O or S;

W, X, or Z are each independently selected from N or CR^1 , CR^2 , or CR^3 , with the proviso that when Y is O and Z is N, then W is CR^1 and X is CR^2 ;

R^1 , R^2 , and R^3 are each independently selected from the following:

H, F, Cl, Br, I, R^{12} , CF_3 , CF_2R^{12} , CF_2CF_2 , CCl_3 , CCl_2R^{12} , $CCl_2CCl_2R^{12}$, $NR^{13}R^{14}$, $NR^{15}COR^{12}$, $NR^{15}SO_2R^{12}$, OR^{12} , OCF_3 , OCF_2R^{12} , $OCF_2CF_2R^{12}$, $OCOR^{12}$, OSO_2R^{12} , $OPO(OR^{12})_2$, SR^{12} , SCF_3 , SCF_2R^{12} , $SCF_2CF_2R^{12}$, $SCOR^{12}$, SO_3R^{12} , $SO_2NR^{13}R^{14}$, $PO(OR^{12})_3$, $PO(OR^{12})_2R^{12}$, NO_2 , CN, $CNR^{15}(NR^{13}R^{14})$, $CNR^{15}(SR^{12})$, $COOR^{12}$, $COSR^{12}$, $CONR^{13}R^{14}$, and

wherein any two adjacent positions of R^1 , R^2 , R^3 , R^4 , and R^5 can be joined by a chain selected from $CHCHCHCH$, $CH_2CH_2CH_2CH_2$, $CHCHCH_2$, $CH_2CH_2CH_2$, CH_2CH_2 , SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure;



R^4 is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, COR^5 , CSR^5 , and SO_2R^5 ;

R^5 , R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^6 and R^7 are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl

R^8 , R^9 , R^{10} , and R^{11} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl and alkylaryl;

R^{12} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl or cycloalkylalkyl, C_{2-8} alkenyl, aryl, alkylaryl, $(CH_2)_nNR_{13}R_{14}$, $(CH_2)_mSO_3H$, and $(CH_2)_mCO_2H$, wherein n is 2 through 6 and m is 1 through 6;

R^{13} and R^{14} are each independently selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or cycloalkylalkyl, or aryl or CH_2 aryl, wherein each said aryl group or said aryl portion of said CH_2 aryl group may be optionally substituted by up to four substituents in any position independently selected from:

F, Cl, Br, I, CF_3 , CCl_3 , CH_3 , C_2H_5 , C_3H_7 , C_4H_9 , NH_2 , $NHCH_3$, $N(CH_3)_2$, NHC_2H_5 , $N(C_2H_5)_2$, NHC_3H_7 , $N(C_3H_7)_2$, NHC_4H_9 , $N(C_4H_9)_2$, $NHCOH$, $NHCOCH_3$,



NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

wherein when R¹³ and/or R¹⁴ contain an aryl ring substituted at two adjacent positions on said aryl ring, then said two adjacent positions can be joined by a chain selected from CHCHCHCH, CH₂CH₂CH₂CH₂, CHCHCH₂, CH₂CH₂CH₂, CH₂CH₂SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; or

R¹³ and R¹⁴ form part of a 5, 6 or 7 membered saturated cyclic structure or 5, 6 or 7 membered unsaturated cyclic structure, each such structure optionally containing up to four heteroatoms selected from O, N and S and wherein each said cyclic structure may be optionally substituted by up to four substituents in any position, each position independently selected from:

F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂,



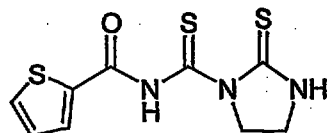
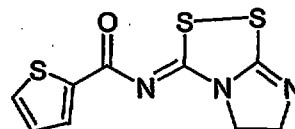
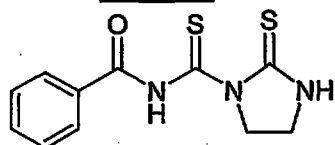
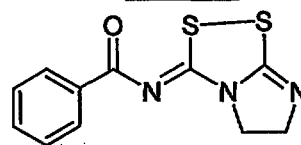
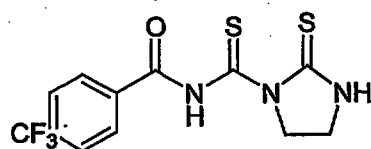
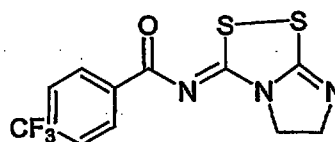
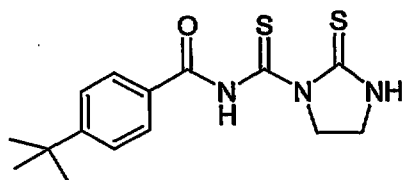
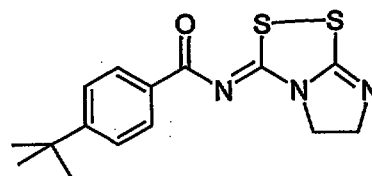
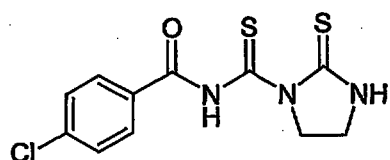
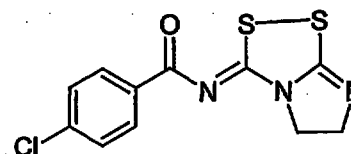
NHCOH , NHCOCH_3 , NHCOC_2H_5 , NHCOC_3H_7 , NHCOC_4H_9 ,
 NHSO_2CH_3 , $\text{NHSO}_2\text{C}_2\text{H}_5$, $\text{NHSO}_2\text{C}_3\text{H}_7$, $\text{NHSO}_2\text{C}_4\text{H}_9$, OH , OCH_3 ,
 OC_2H_5 , OC_3H_7 , OC_4H_9 , OC_5H_{11} , OC_6H_{13} ,
 OCF_3 , OCOCH_3 , OCOC_2H_5 , OCOC_3H_7 , OCOC_4H_9 , OSO_2CH_3 ,
 $\text{OSO}_2\text{C}_2\text{H}_5$, $\text{OSO}_2\text{C}_3\text{H}_7$, $\text{OSO}_2\text{C}_4\text{H}_9$, SH , SCH_3 , SC_2H_5 , SC_3H_7 , SC_4H_9 ,
 SC_5H_{11} , SC_6H_{13} , SCF_3 , SCOCH_3 , SCOC_2H_5 ,
 SCOC_3H_7 , SCOC_4H_9 , SO_3CH_3 , $\text{SO}_3\text{C}_2\text{H}_5$, $\text{SO}_3\text{C}_3\text{H}_7$, $\text{SO}_3\text{C}_4\text{H}_9$,
 SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{NHC}_2\text{H}_5$, $\text{SO}_2\text{N}(\text{C}_2\text{H}_5)_2$,
 $\text{SO}_2\text{NHC}_3\text{H}_7$, $\text{SO}_2\text{N}(\text{C}_3\text{H}_7)_2$, $\text{SO}_2\text{NHC}_4\text{H}_9$, $\text{SO}_2\text{N}(\text{C}_4\text{H}_9)_2$, NO_2 , CN ,
 COOCH_3 , COOC_2H_5 , COOC_3H_7 , COOC_4H_9 , COSCH_3 , COSC_2H_5 ,
 COSC_3H_7 , COSC_4H_9 , CONH_2 , CONHCH_3 , $\text{CON}(\text{CH}_3)_2$, CONHC_2H_5 ,
 $\text{CON}(\text{C}_2\text{H}_5)_2$, CONHC_3H_7 , $\text{CON}(\text{C}_3\text{H}_7)_2$, CONHC_4H_9 , $\text{CON}(\text{C}_4\text{H}_9)_2$,
 and

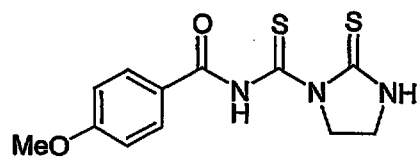
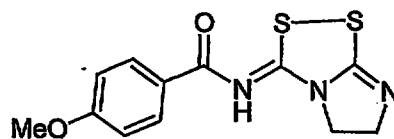
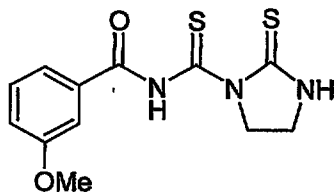
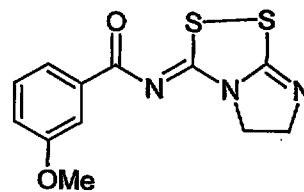
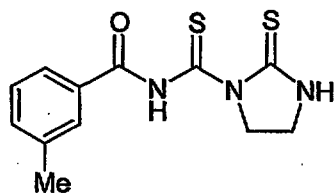
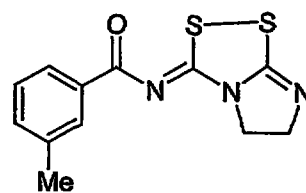
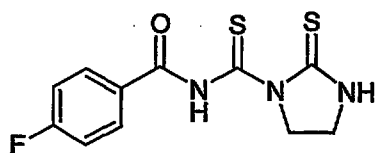
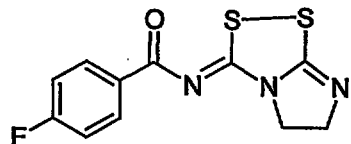
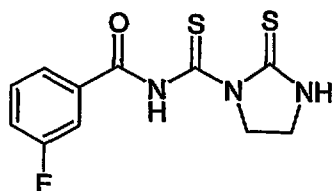
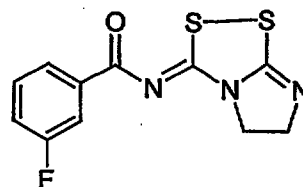
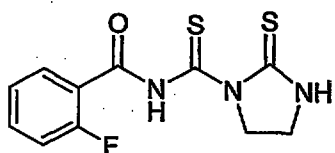
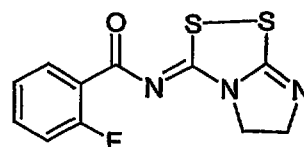
wherein when R^{13} and R^{14} form an aryl ring substituted at two adjacent
 positions on said aryl ring, then said two adjacent positions can be joined by a
 chain selected from CHCHCHCH , $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, CHCHCH_2 ,
 $\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{SCH}_2\text{S}$, $\text{SCH}_2\text{CH}_2\text{S}$, OCH_2O , and $\text{OCH}_2\text{CH}_2\text{O}$ to form
 a bi-cyclic structure; and

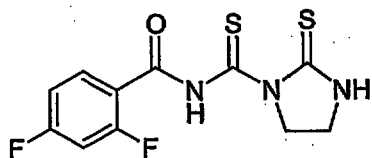
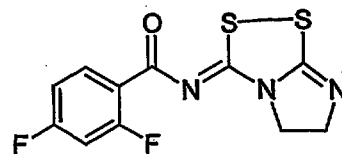
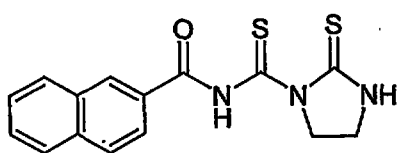
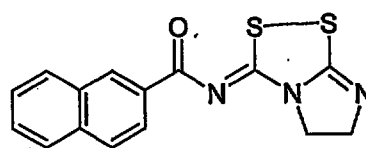
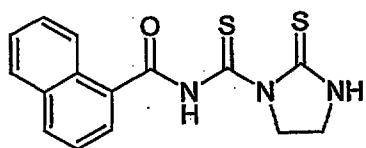
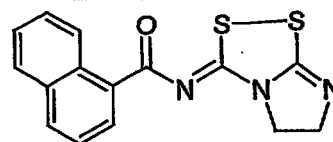
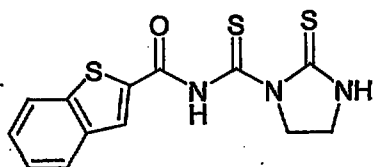
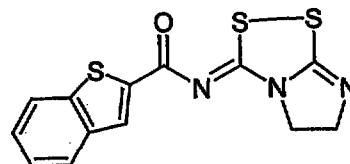
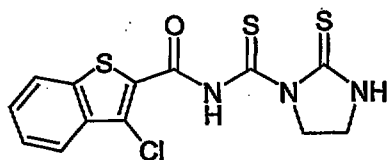
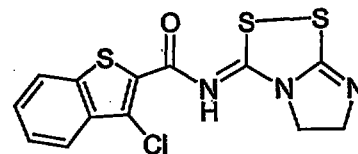
R^{15} is selected from H, C_{1-8} straight chain alkyl, branched alkyl, C_{3-8} cycloalkyl, C_{4-9}
 alkylcycloalkyl or cycloalkylalkyl, and C_{2-8} alkenyl.

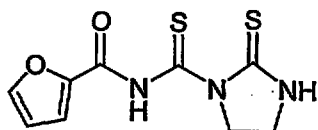
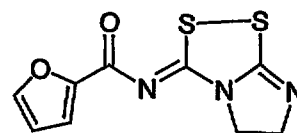
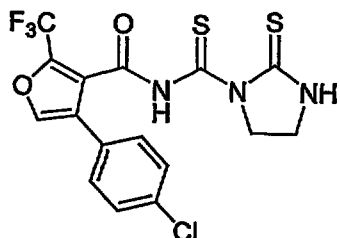
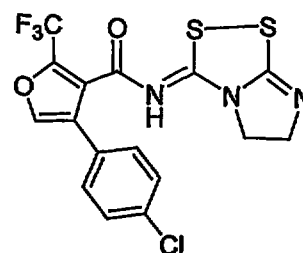
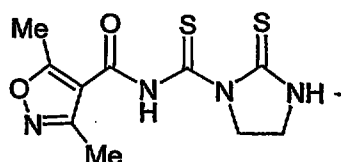
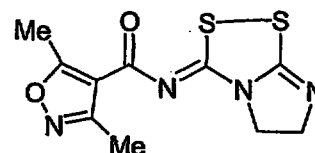
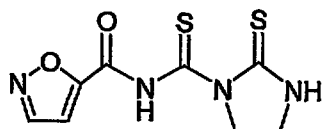
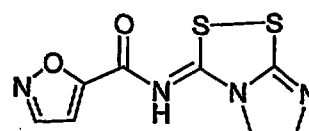
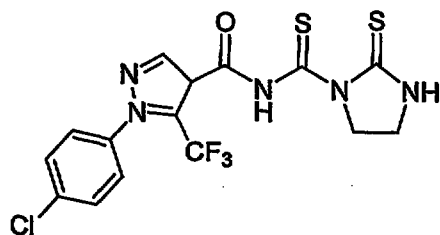
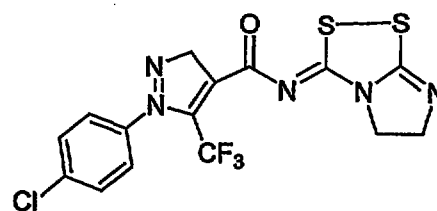
19. A small molecule, GPR6 inverse agonist selected from the group consisting of the following structures:

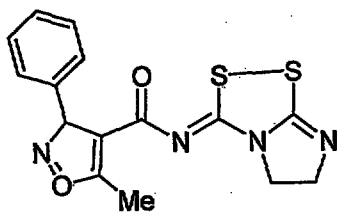
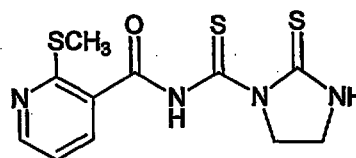
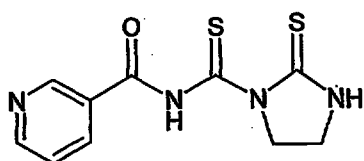
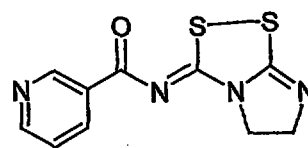


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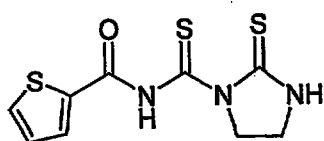
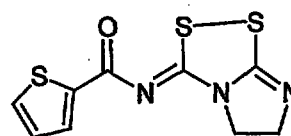
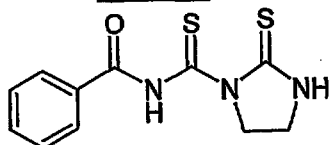
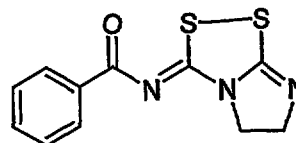
ARE121ARE122ARE123ARE124ARE125ARE126ARE127ARE128ARE129ARE130ARE131ARE132

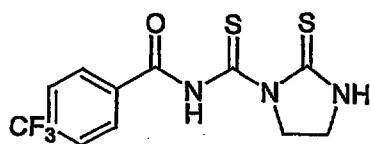
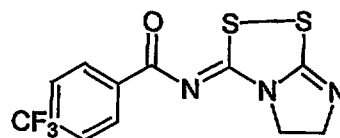
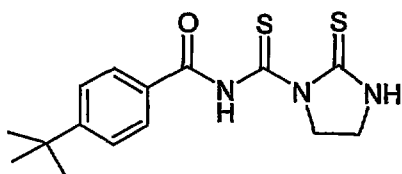
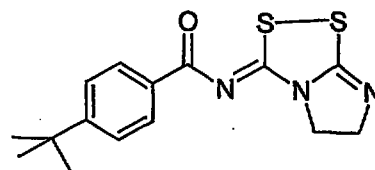
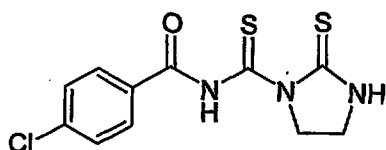
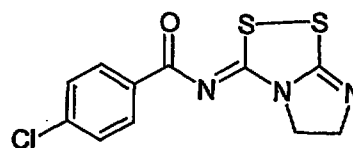
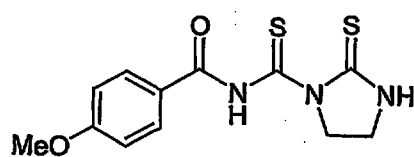
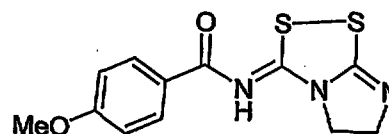
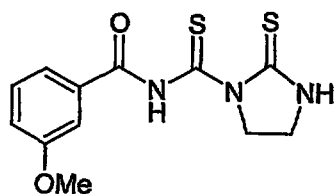
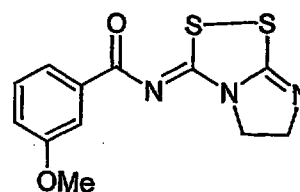
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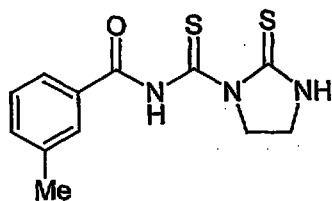
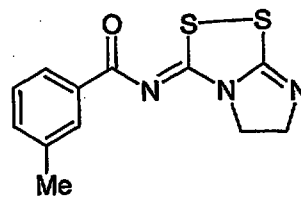
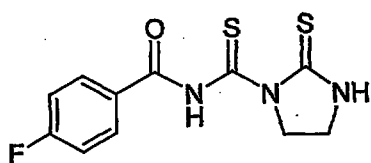
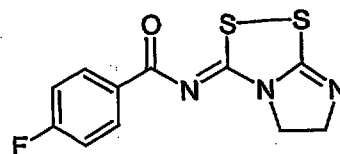
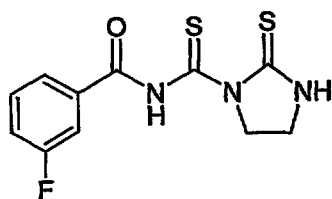
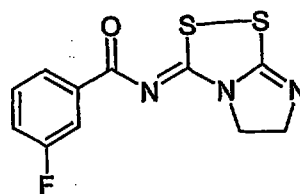
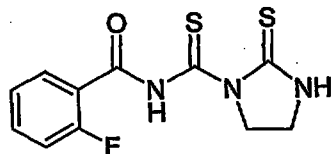
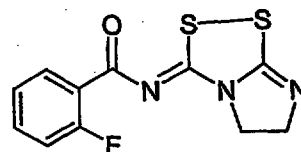
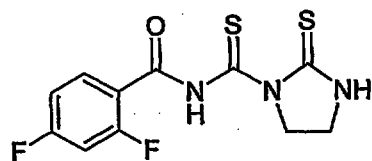
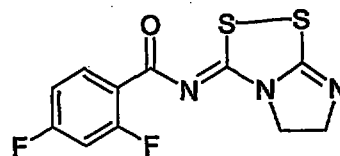
ARE143ARE144ARE145ARE146ARE147ARE148ARE149ARE150ARE151ARE152

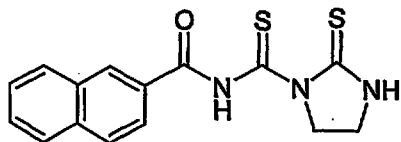
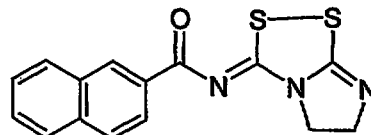
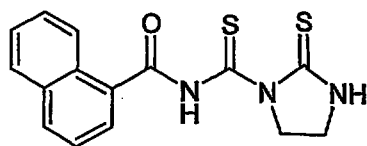
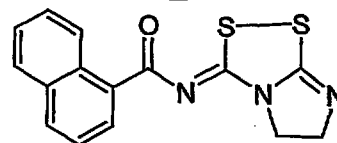
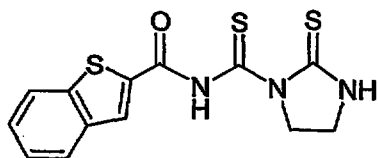
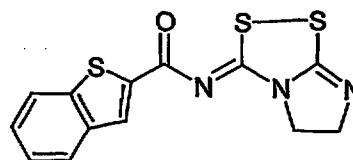
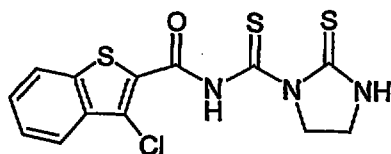
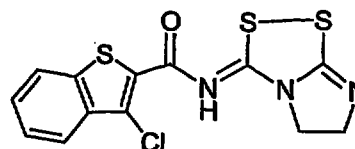
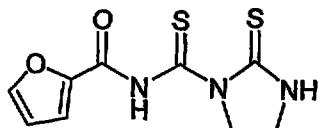
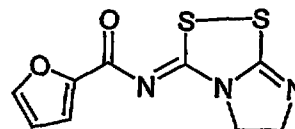
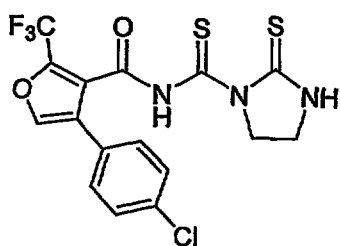
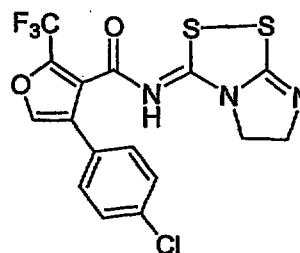
ARE153ARE154ARE155ARE156

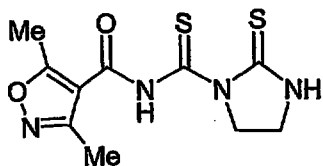
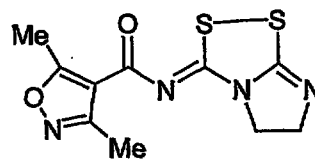
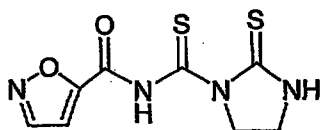
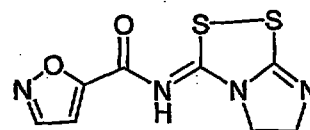
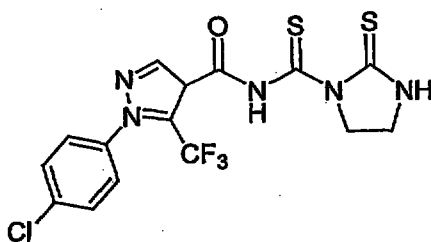
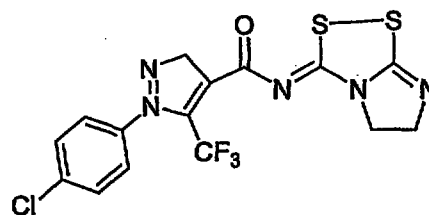
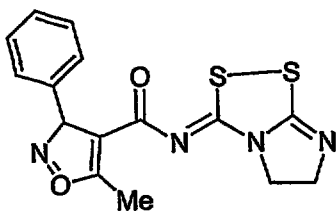
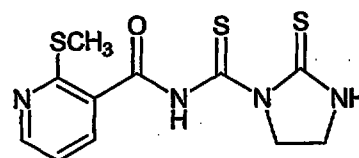
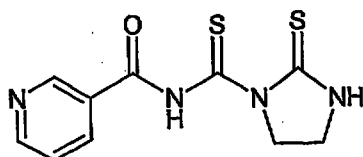
20. A method for modulating by inverse agonism the G protein-coupled receptor, GPR6, comprising the step of contacting GPR6 with a small molecule GPR6 inverse agonist selected from the group consisting of:

ARE111ARE112ARE113ARE114

ARE115ARE116ARE117ARE118ARE119ARE120ARE121ARE122ARE123ARE124

ARE125ARE126ARE127ARE128ARE129ARE130ARE131ARE132ARE133ARE134

ARE135ARE136ARE137ARE138ARE139ARE140ARE141ARE142ARE143ARE144ARE145ARE146

ARE147ARE148ARE149ARE150ARE151ARE152ARE153ARE154ARE155ARE156