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(54) Title: HTR1<sub>D</sub> INHIBITORS AND USES THEREOF IN THE TREATMENT OF CANCER

(57) Abstract: The present invention deals with a 5 -hydroxytryptamine receptor 1D (5-HTR1<sub>D</sub>) inhibitor and with a combination of a 5-HTR1<sub>D</sub> inhibitor and at least one inhibitor of 5 -hydroxytryptamine receptor 1B (5-HTR1<sub>B</sub>) for use in the prevention and/or treatment of cancer in a subject in need thereof. According to the invention the cancer may be selected from the group comprising breast cancer, liver cancer, lung cancer, brain cancer, mesothelioma, head and neck squamous cell carcinoma, kidney cancer, gastric cancer and cervix cancer.



WO 2020/183011 A1

## HTR1<sub>D</sub> INHIBITORS AND USES THEREOF IN THE TREATMENT OF CANCER

### FIELD OF INVENTION

- 5 The present invention relates to the treatment of cancer. In particular, the present invention relates to the use of 5-hydroxytryptamine receptor 1D inhibitors in the prevention and treatment of cancer. The present invention further relates to the use of 5-hydroxytryptamine receptor 1D inhibitors in combination with one or several 5-hydroxytryptamine receptor 1B inhibitor(s) in the prevention and treatment of cancer.
- 10 The present invention further pertains to diagnosis, stratification and/or prognosis methods based on the measure of HTR1D and/or HTR1B gene expression level.

### BACKGROUND OF INVENTION

- Breast cancer is a cancer that develops from breast tissue. Most breast cancers are
- 15 invasive, *i.e.*, the proliferation of cell has expanded into surrounding breast tissues, beyond the wall of the glands or ducts where they originate from. The extent of the spread of the cancer at the time of diagnosis is used in the TNM (Tissue, Node, Metastasis) staging system, that distinguishes between five stages of advancement, from noninvasive (stage 0) to metastasized cancer (stage IV).

- 20 In addition to the TNM classification, several molecular markers have recently been identified, allowing the distinction of four main types of cancer. This classification is based on the presence or absence of hormone receptors for progesterone and estrogen (HR<sup>+</sup> vs HR<sup>-</sup>) and of epidermal growth factor receptor 2 (HER2<sup>+</sup> vs HER2<sup>-</sup>).

The four types of breast cancer are:

- 25 - **HR<sup>-</sup>/HER2<sup>+</sup>**. This type of cancer, called “HER2-enriched breast cancer”, accounts for about 1 to 5% of all diagnosed breast cancers. Despite the tendency of cancer in this group to grow and spread aggressively, the use of targeted therapies has reversed much of the adverse prognosis impact of HER2

overexpression. Because of the absence of hormone receptors, HER2-enriched breast cancers do not respond to hormonal therapy. Targeted therapies are therefore used, such as Herceptin (trastuzumab), Perjeta (pertuzumab), Tykerb (lapatinib) or Kadcyła (T-DM1 or ado-trastuzumab emtansine).

- 5       - **HR<sup>+</sup>/HER2<sup>-</sup>**. This type of breast cancers, called “luminal A breast cancer”, is the most common form of breast cancer. It accounts for around 70 to 75% of all diagnosed breast cancers. Luminal A breast cancers have low levels of proliferation marker Ki-67, which helps control how fast cancer cells grow. Luminal A cancers tend to be slow-growing, low-grade and thus less aggressive. They are thus associated with favorable prognosis and good response to hormonal therapy.
- 10       - **HR<sup>+</sup>/HER2<sup>+</sup>**. This type of breast cancers, called “luminal B breast cancer”, is further defined by being highly positive for the proliferation marker Ki-67. It accounts for around 10% of all diagnosed breast cancers and tends to be higher-grade and more aggressive than luminal A breast cancers.
- 15       - **HR<sup>-</sup>/HER2<sup>-</sup>**. This last group of breast cancers, called “triple negative breast cancer” (as they are negative for both hormone receptors and HER2), accounts for about 12 to 15% of all diagnosed breast cancers. They have the poorest short-term prognosis as they are the most aggressive subtype, associated with a large risk for early distant metastasis and for which there is currently no targeted therapy. Interestingly, this type of cancer is more common in women with *BRCA1* gene mutations. It has also been shown that it is the most common type of breast cancers among young women.
- 20

Recently, serotonin (5-hydroxytryptamine or 5-HT) has emerged as an important  
25 regulator of cell proliferation and tumor growth in a variety of tissues. 5-HT, well studied for its function in the nervous system as neurotransmitter, has numerous important peripheral functions. Of particular interest in the context of cancer, 5-HT has been shown to function as a growth factor regulating normal cell (*e.g.*, vascular smooth muscle cells, lung fibroblasts, mammary epithelial cells or renal mesangial cells) and cancer cell  
30 (*e.g.*, in cholangiocarcinoma, breast cancer, bladder cancer or pancreatic cancer) proliferation in various tissues (Nemecek *et al.*, 1986. *Proc Natl Acad Sci U S A*.

**83(3)**:674-8; Takuwa *et al.*, **1989**. *Am J Physiol.* **257(3 Pt 2)**:F431-9; Soll *et al.*, **2010**. *Hepatology.* **51(4)**:1244-54; Pai *et al.*, **2009**. *Breast Cancer Res.* **11(6)**:R81; Gurbuz *et al.*, **2014**. *PLoS One.* **9(9)**:e110067).

5 5-HT can exert its action through a repertoire of more than 15 G protein-coupled receptors or ligand-gated ion channels, collectively named 5-HT receptors, and belonging to seven families: 5-HTR1 to 7. Another major player in the 5-HT system, primarily terminating the action of 5-HT, is the 5-HT reuptake transporter (SERT, encoded by the *SLC6A4* gene). Of note, another 5-HT transporter has been identified, which may account for a significant percentage of 5-HT clearance although having a low serotonergic affinity  
10 (Zhou *et al.*, **2007**. *Biochem Pharmacol.* **73(1)**:147-54).

In short, the large number of potential receptors and the numerous physiological processes in which the 5-HT machinery is involved has hampered the identification of target(s) that would be of interest in the treatment of cancer.

In an attempt to circumvent this limitation, International patent application  
15 WO2013063492 reports the downregulation of cell proliferation, colony formation and the induction of apoptosis in breast cancer cell models using the selective 5-HTR1<sub>B</sub> receptor antagonists SB224289 and SB216641. Curiously however, the same disclosure shows a similar antiproliferative effect of 5-nonyltryptamine (5-NT), a triptan (*i.e.*, a class of molecules known as 5-HTR1<sub>B</sub> agonists), on breast cancer cell models.

20 In view of these observations, it remains unclear whether an efficient therapeutic approach in the treatment of breast cancer requires to downregulate or upregulate 5-HTR1<sub>B</sub> signaling activity. While these observations point toward a role for serotonin and associated signaling pathways in the regulation of breast tissues homeostasis in normal and pathological conditions, there is a lack of evidence allowing to choose the  
25 best target and the best approach for the treatment of breast cancer.

Here, the Inventors show that the expression of the gene coding for 5-HTR1<sub>D</sub>, *HTR1D*, is upregulated in breast cancer patient with poor prognosis. From this finding, the Inventors further demonstrate that inhibiting 5-HTR1<sub>D</sub> signaling, either by using a selective 5-HTR1<sub>D</sub> antagonist or a specific silencing RNA (siRNA), decreases breast cancer cell



viability. Moreover, they show that this decrease in breast cancer cell viability is even sharper when both 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub> signaling are inhibited. Together, these observations unveil a novel therapeutic strategy for breast cancer patients, *i.e.*, the inhibition of 5-HTR1<sub>D</sub> signaling alone or in combination with the inhibition of 5-HTR1<sub>B</sub> signaling.

Interestingly, the association of higher level of *HTR1D* expression and poor prognosis seen in breast cancer has also been observed by the Inventors in several other cancers: liver cancer, lung cancer, brain lower grade glioma, mesothelioma, head and neck squamous cell carcinoma, renal clear cell carcinoma, renal chromophobe cell carcinoma, renal papillary cell carcinoma, gastric cancer and cervical squamous cell carcinoma. This suggests a more global therapeutic effect of 5-HTR1<sub>D</sub> signaling inhibition for the treatment of cancers, beyond breast cancer.

## SUMMARY

According to a first aspect, the invention deals with a 5-hydroxytryptamine receptor 1<sub>D</sub> (5-HTR1<sub>D</sub>) inhibitor, for use in the prevention and/or treatment of cancer in a subject in need thereof.

In a first embodiment of the invention, the 5-HTR1<sub>D</sub> inhibitor is selected from the group comprising small organic molecules, antibodies, aptamers and polynucleotides.

In a further embodiment of the invention, the 5-HTR1<sub>D</sub> inhibitor is a selective 5-HTR1<sub>D</sub> inhibitor.

According to another aspect, the invention deals with a combination of at least one 5-HTR1<sub>D</sub> inhibitor and at least one inhibitor of 5-hydroxytryptamine receptor 1<sub>B</sub> (5-HTR1<sub>B</sub>) for use in the prevention and/or treatment of cancer in a subject in need thereof wherein said 5-HTR1<sub>D</sub> inhibitor and/or 5-HTR1<sub>B</sub> is preferably selected from the group comprising small organic molecules, antibodies, aptamers and polynucleotides.

According to another aspect, the invention deals with a composition for use in the prevention and/or treatment of cancer in a subject in need thereof, comprising a 5-HTR<sub>1D</sub> inhibitor as above described

According to further aspect, the composition for use further comprises at least one  
5 inhibitor of 5-hydroxytryptamine receptor 1B (5-HTR<sub>1B</sub>).

In a further embodiment of the invention, the 5-HTR<sub>1B</sub> inhibitor of said composition for use is selected from the group comprising small organic molecules, antibodies, aptamers and polynucleotides.

In a further embodiment of the invention, the composition for use is a pharmaceutical  
10 composition comprising at least one pharmaceutically acceptable excipient.

In a further embodiment of the invention, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition is for use in the treatment and/or prevention of cancer, wherein said cancer is selected from the group comprising breast cancer, liver cancer, lung cancer, brain cancer, mesothelioma, head and neck squamous cell carcinoma, kidney cancer, gastric  
15 cancer and cervix cancer.

In a still further embodiment, said cancer is selected from the group comprising breast cancer, liver cancer, lung cancer, brain cancer and mesothelioma.

In a still further embodiment, said cancer cells overexpress the gene coding for 5-HTR<sub>1D</sub>.

In a still further embodiment, said cancer cells overexpress the gene coding for 5-HTR<sub>1B</sub>.

20 In a still further embodiment the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition is for use in the treatment and/or prevention of breast cancer preferably triple negative, HER2-enriched, luminal B or luminal A breast cancer

The present invention also deals with a medicament comprising the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition of the present invention, for use in the treatment and/or  
25 prevention of cancer, wherein said cancer is selected from the group comprising breast cancer, liver cancer, lung cancer, brain cancer, mesothelioma, head and neck squamous

cell carcinoma, kidney cancer, gastric cancer and cervix cancer, more particularly breast cancer and preferably triple negative, HER2-enriched, luminal B or luminal A breast cancer

The present invention also deals with an *in vitro* cancer diagnosis, stratification and/or  
5 prognosis method comprising a step of measuring the expression level of 5-HTR1<sub>D</sub>  
and/or 5-HTR1<sub>B</sub> in a sample previously obtained from a subject.

## DEFINITIONS

In the present invention, the following terms have the following meanings:

10 “**5-hydroxytryptamine receptor 1B**” or “**5-HTR1<sub>B</sub>**”, as used herein, have their general  
meaning in the art and refer to a seven-pass transmembrane G protein-coupled receptor.  
Its natural ligand is serotonin (5-HT), and its principal signal transduction pathway is  
cyclic-AMP. Briefly, upon binding of serotonin to 5-HTR1<sub>B</sub>, a conformational change  
allows it to act as a guanine nucleotide exchange factor. The receptor can then activate the  
15 associated G<sub>αi</sub> protein by exchanging the GDP bound to the G protein for a GTP, thereby  
inhibiting cyclic AMP synthesis by the adenylate cyclase. In human, 5-HTR1<sub>B</sub> is a  
390-amino acid protein with SEQ ID NO: 33, encoded by the *HTR1B* gene. It shares  
60.6% global identity with SEQ ID NO: 34 (5-HTR1<sub>D</sub>) as assessed by EMBOSS Needle  
and 67.1% local identity with SEQ ID NO: 34 (5-HTR1<sub>D</sub>) as assessed by EMBOSS  
20 Water.

“**5-hydroxytryptamine receptor 1D**” or “**5-HTR1<sub>D</sub>**”, as used herein, have their general  
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Its natural ligand is serotonin (5-HT), and its principal signal transduction pathway is  
cyclic-AMP. Briefly, upon binding of serotonin to 5-HTR1<sub>D</sub>, a conformational change  
25 allows it to act as a guanine nucleotide exchange factor. The receptor can then activate the  
associated G<sub>αi</sub> protein by exchanging the GDP bound to the G protein for a GTP hereby  
inhibiting cyclic AMP synthesis by the adenylate cyclase. It shares 60.6% global identity  
with SEQ ID NO: 33 (5-HTR1<sub>B</sub>) as assessed by EMBOSS Needle and 67.1% local  
identity with SEQ ID NO: 33 (5-HTR1<sub>B</sub>) as assessed by EMBOSS Water.

“**5-HTR1<sub>D</sub> inhibitor**” and “**5-HTR1<sub>B</sub> inhibitor**”, as used herein, both refer to any molecule, compound or substance that, when administered to a subject, leads to a partial or complete reduction of the normal physiological activity of 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub>, respectively. By normal physiological activity of 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub> is meant the physiological activity of these receptors which is observed upon binding of their natural ligand, 5-HT. These terms also refer to any molecule, compound or substance that, when administered to a subject, leads to a reversal of the normal physiological activity of 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub>, respectively (*i.e.*, to a physiological activity which is opposite to the normal physiological activity of these receptors which is observed upon binding of their natural ligand, 5-HT). For example, but without limitation, inhibition can be achieved by preventing the binding of 5-HT to 5-HTR1<sub>D</sub> or 5-HTR1<sub>B</sub> using a receptor antagonist; by preventing the synthesis of 5-HTR1<sub>D</sub> or 5-HTR1<sub>B</sub>; or by inducing a physiological activity which is opposite to the normal physiological activity which is observed upon binding of 5-HT, using a receptor inverse agonist.

“**Antibody**”, as used herein, encompasses intact polyclonal antibodies, intact monoclonal antibodies, single-domain antibodies, nanobodies, antibody fragments (such as Fab, Fab', F(ab')<sub>2</sub> and Fv fragments), single chain Fv (scFv) mutants, multispecific antibodies (such as bispecific antibodies generated from at least two intact antibodies), chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antigen determination portion of an antibody, and any other modified immunoglobulin molecule comprising an antigen recognition site, so long as the antibodies exhibit the desired biological activity. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as  $\alpha$  (alpha),  $\delta$  (delta),  $\epsilon$  (epsilon),  $\gamma$  (gamma) and  $\mu$  (mu), respectively. The different classes of immunoglobulins have different and well-known subunit structures and three-dimensional configurations. Antibodies can be naked, or conjugated to other molecules such as toxins, radioisotopes, or any of the other specific molecules recited herein. A “**monoclonal antibody**” refers to a homogeneous antibody population involved in the highly specific recognition and binding of a single antigenic determinant or epitope. This is in contrast to “**polyclonal antibodies**” that typically

include different antibodies directed against different antigenic determinants. The term “**monoclonal antibody**” encompasses both intact and full-length monoclonal antibodies, as well as antibody fragments (such as Fab, Fab’, F(ab’)<sub>2</sub>, Fv), single chain (scFv) mutants, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antigen recognition site. Furthermore, “**monoclonal antibody**” refers to such antibodies made in any number of ways including, but not limited to, by hybridoma, phage selection, recombinant expression, and transgenic animals. The term “**humanized antibody**” refers to an antibody derived from a non-human (*e.g.*, murine) immunoglobulin, which has been engineered to contain minimal non-human (*e.g.*, murine) sequences. Typically, humanized antibodies are human immunoglobulins in which residues from the complementary determining region (CDR) are replaced by residues from the CDR of a non-human species (*e.g.*, mouse, rat, rabbit, or hamster) that have the desired specificity, affinity, and capability (Jones *et al.*, 1986. *Nature*. **321(6069)**:522-5; Riechmann *et al.*, 1988. *Nature*. **332(6162)**:323-7; Verhoeven *et al.*, 1988. *Science*. **239(4847)**:1534-6). In some instances, the Fv framework region (FW) residues of a human immunoglobulin are replaced with the corresponding residues in an antibody from a non-human species that has the desired specificity, affinity and capability. Humanized antibodies can be further modified by the substitution of additional residues either in the Fv framework region and/or within the replaced non-human residues to refine and optimize antibody specificity, affinity, and/or capability. In general, humanized antibodies will comprise substantially all of at least one, and typically two or three, variable domains containing all or substantially all of the CDR regions that correspond to the non- human immunoglobulin whereas all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. Humanized antibody can also comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Examples of methods used to generate humanized antibodies are described in US Patents US5,225,539 and US5,639,641.

“**Aptamer**”, as used herein, refers to a class of molecule that represents an alternative to antibodies in term of molecular recognition. Aptamers are oligonucleotide or oligopeptide sequences with the capacity to recognize virtually any class of target molecules with high

affinity and specificity. Such ligands may be isolated through Systematic Evolution of Ligands by EXponential enrichment (SELEX) of a random sequence library, as described in Tuerk *et al.* (1990. *Science*. **249**(4968):505-10). The random sequence library is obtainable by combinatorial chemical synthesis of DNA. In this library, each member is  
5 a linear oligomer, eventually chemically modified, of a unique sequence. Possible modifications, uses and advantages of this class of molecules have been reviewed by Jayasena (1999. *Clin Chem*. **45**(9):1628-50). Peptide aptamers consists of a conformationally constrained antibody variable region displayed by a platform protein, such as *E. coli* thioredoxin A, that are selected from combinatorial libraries by two hybrid  
10 methods (Colas *et al.*, 1996. *Nature*. **380**(6574):548-50).

“**Cancer**”, as used herein, refers to any member of a class of diseases or disorders characterized by uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis. Metastasis is defined as the stage in which cancer cells  
15 are transported through the bloodstream or lymphatic system. Cancers are classified by the type of cell that the tumor resembles and, therefore, the tissue presumed to be the origin of the tumor. For example, carcinomas are malignant tumors derived from epithelial cells. This group represents the most common cancers, including the common forms of breast, prostate, lung, and colon cancer. Lymphomas and leukemias include  
20 malignant tumors derived from blood and bone marrow cells. Sarcomas are malignant tumors derived from connective tissue or mesenchymal cells. Mesotheliomas are tumors derived from the mesothelial cells lining the peritoneum and the pleura. Gliomas are tumors derived from glia, the most common type of brain cell. Germinomas are tumors derived from germ cells, normally found in the testicle and ovary. Choriocarcinomas are  
25 malignant tumors derived from the placenta. Specific, non-limiting examples of cancer cells whose proliferation is reduced by the inhibitors or composition of the present invention include breast cancer (including HER2-enriched breast cancer, luminal A breast cancer, luminal B breast cancer and triple negative breast cancer), liver cancer (including liver hepatocellular carcinoma), lung cancer (including lung adenocarcinoma), pancreas  
30 cancer, brain cancer (including brain lower-grade glioma), mesothelioma, head and neck squamous cell carcinoma, kidney cancer (including clear renal cell carcinoma,

chromophobe renal cell carcinoma and papillary renal cell carcinoma), gastric cancer and cervical cancer.

“**Expression**”, as used herein, refers to the expression of a gene. Expression of a gene may be determined at the protein level by ways of, *e.g.*, immunohistochemistry, Multiplex  
5 methods (Luminex), western blot, enzyme-linked immunosorbent assay (ELISA), sandwich ELISA, fluorescent-linked immunosorbent assay (FLISA), enzyme immunoassay (EIA), radioimmunoassay (RIA) and the like. Alternatively, expression of a gene may be determined at the mRNA level, by ways of, *e.g.*, RT-PCR, RT-qPCR (wherein qPCR stands for quantitative PCR), hybridization techniques such as, for  
10 example, Northern Blot, use of microarrays, and combination thereof including but not limited to, hybridization of amplicons obtained by RT-PCR, sequencing such as, for example, next-generation DNA sequencing (NGS) or RNA-seq (also known as “Whole Transcriptome Shotgun Sequencing”) and the like.

“**Overexpression**” as used herein, refers to the expression of a gene being higher in a  
15 sample when compared to a “**reference expression level**”. The reference expression level can be the typical level of expression observed in a similar population of cancer cell among a large group of subjects (typically more than 10, preferably at least 50 or more subjects). The reference expression level can also refer to the level of expression in healthy cells of the same tissue of origin in the same subject or derived from a large group  
20 of subjects. The reference expression level can also refer also the level of expression in the cancer cells of a subject at different time points. The person of the art is familiar with the techniques allowing the comparison of gene expression level.

“**Receptor antagonist**”, as used herein, refers to any molecule, compound or substance that binds to a receptor and thereby prevents the normal physiological activity which is  
25 observed upon binding of its activating ligand (*i.e.*, the receptor agonist). A receptor antagonist can, for instance, compete with the binding of the agonist to the receptor.

“**Receptor inverse agonist**”, as used herein refers to any molecule, compound or substance that binds to the same receptor as the receptor agonist but exerts the opposite effect. Receptor inverse agonists have the ability to decrease the constitutive activity of  
30 the receptor, *i.e.*, the basal receptor activity observed in absence of receptor agonist.

“**Response to chemotherapy**”, as used herein refers to the effectiveness of a chemotherapy in treating a cancer. Methods to measure the effectiveness of a chemotherapy as known in the art and includes, but is not limited to, determining the size of a solid tumor, metabolites level reflecting the function of the organ(s) affected by cancer, measuring the level of a cancer marker and cell counting techniques. A subject  
5 having cancer can be “resistant to chemotherapy” or “unresponsive to chemotherapy” if, after chemotherapy, said cancer as progressed, remained stable or insufficiently decreased. Alternatively, a subject having cancer can be “responsive to chemotherapy” if, after chemotherapy, said cancer has become undetectable or has significantly  
10 decreased.

“**Treatment**”, as used herein, refers to both therapeutic and prophylactic (or preventive) measures, whose object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be  
15 prevented. A subject or mammal is successfully “treated” if, after receiving a therapeutic amount of the inhibitor or composition according to the present invention, the patient shows one or more of the following observable and/or measurable changes: amelioration related to one or more of the symptoms associated with the specific disease or condition, reduction of morbidity and mortality and improvement in quality of life issues. Example  
20 of observable or measurable changes includes, but are not limited to, a reduction of the cancer cells proliferation, a decrease in the size or a disappearance of the tumor, the prevention of metastasis or recurrence, a reduction in the appearance of tumors and an increase of cancer cell death. The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to  
25 a physician.

“**Therapeutically effective amount**”, as used herein, refers to the level or amount of the inhibitor or composition according to the present invention, that is aimed at (but without causing significant negative or adverse side effects to the subject): (1) delaying or preventing the onset of the targeted condition or disorder; (2) slowing down or stopping  
30 the progression, aggravation, or deterioration of one or more symptoms of the targeted condition or disorder; (3) bringing about ameliorations of the symptoms of the targeted



condition or disorder; (4) reducing the severity or incidence of the targeted condition or disorder; and/or (5) curing the targeted condition or disorder. A therapeutically effective amount of the inhibitor or composition according to the present invention may be administered prior to the onset of the targeted condition or disorder, for a prophylactic or preventive action. Alternatively or additionally, the therapeutically effective amount of the inhibitor or composition according to the present invention may be administered after initiation of the targeted condition or disorder, for a therapeutic action.

“**Subject**”, as used herein, refers to a warm-blooded animal, preferably a human, a pet or livestock. As used herein, the terms “**pet**” and “**livestock**” include, but are not limited to, dogs, cats, guinea pigs, rabbits, pigs, cattle, sheep, goats, horses and poultry. In some embodiments, the subject is a male or female subject. In some embodiments, the subject is an adult (for example, a subject above the age of 18 (in human years) or a subject after reproductive capacity has been attained). In some embodiments, the subject may be a “**patient**”, *i.e.*, a subject who/which is awaiting the receipt of or is receiving medical care or was/is/will be the object of a medical procedure according to the methods of the present invention or is monitored for the development of a disease.

## DETAILED DESCRIPTION

The present invention relates to a 5-hydroxytryptamine receptor 1D (5-HTR1<sub>D</sub>) inhibitor, for use in the prevention and/or treatment of cancer in a subject in need thereof.

In one embodiment, 5-HTR1<sub>D</sub> inhibitors according to the present invention include, but are not limited to, small organic molecules, antibodies, aptamers and polynucleotides.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is a selective 5-HTR1<sub>D</sub> inhibitor. By “**selective**”, it is meant that the affinity of the antagonist for 5-HTR1<sub>D</sub> is at least 2-fold, 5-fold, 10-fold, 15-fold, 20-fold, 25-fold, 50-fold, 100-fold or more higher than the affinity for the other human 5-HT receptor (5-HTR1<sub>A</sub>, 5-HTR1<sub>B</sub>, 5-HTR1<sub>C</sub>, 5-HTR1<sub>E</sub>, 5-HTR1<sub>F</sub>, 5-HTR2, 5-HTR3, 5-HTR4, 5-HTR5, 5-HTR6, 5-HTR7).

The affinity of a 5-HTR<sub>1D</sub> inhibitor may be quantified by measuring the activity of 5-HTR<sub>1D</sub> in the presence of a range of concentrations of said inhibitor in order to establish a dose-response curve. From that dose response curve, an IC<sub>50</sub> value may be deduced which represents the concentration of inhibitor necessary to inhibit 50% of the response to an agonist (*e.g.*, 5-HT) in defined concentration. The IC<sub>50</sub> value may be readily determined by the one skilled in the art by fitting the dose-response plots with a dose-response equation as described in De Lean A. & Rodbard D. (1979) *Kinetics of cooperative binding*. In: O'Brien R.D. (eds) *General Principles and Procedures. The Receptors (A Comprehensive Treatise)*, Vol. 1. Springer, Boston, MA. IC<sub>50</sub> values can be converted into affinity constant (K<sub>i</sub>) using the assumptions of Cheng & Prusoff (1973. *Biochem Pharmacol.* **22**(23):3099-108).

Accordingly, a selective 5-HTR<sub>1D</sub> inhibitor is a compound for which at least one of the ratios:

- (i) K<sub>i</sub>(5-HTR<sub>1-7</sub>\5-HTR<sub>1D</sub>):K<sub>i</sub>(5-HTR<sub>1D</sub>), and/or
- (ii) IC<sub>50</sub>(5-HTR<sub>1-7</sub>\5-HTR<sub>1D</sub>):IC<sub>50</sub>(5-HTR<sub>1D</sub>),

is above 2:1, 5:1, 10:1, 15:1, 20:1, 25:1, 50:1, 100:1 or above,

wherein "5-HTR<sub>1-7</sub>\5-HTR<sub>1D</sub>" means all 5-HT receptors except 5-HTR<sub>1D</sub>, *i.e.*, 5-HTR<sub>1A</sub>, 5-HTR<sub>1B</sub>, 5-HTR<sub>1C</sub>, 5-HTR<sub>1E</sub>, 5-HTR<sub>1F</sub>, 5-HTR<sub>2</sub>, 5-HTR<sub>3</sub>, 5-HTR<sub>4</sub>, 5-HTR<sub>5</sub>, 5-HTR<sub>6</sub> and 5-HTR<sub>7</sub>.

Accordingly, a selective 5-HTR<sub>1D</sub> inhibitor is a compound for which at least one of the ratios:

- (i) K<sub>i</sub>(5-HTR<sub>1B</sub>):K<sub>i</sub>(5-HTR<sub>1D</sub>), and/or
- (ii) IC<sub>50</sub>(5-HTR<sub>1B</sub>):IC<sub>50</sub>(5-HTR<sub>1D</sub>),

is above 2:1, 5:1, 10:1, 15:1, 20:1, 25:1, 50:1, 100:1 or above.

In a first embodiment, the 5-HTR<sub>1D</sub> inhibitor is a small organic molecule.

"**Small organic molecule**", as used herein, refers to a molecule of a size comparable to those organic molecules generally used in pharmaceuticals. The term excludes biological macromolecules such as protein and nucleic acids. Preferred small organic molecules

range in size up to about 5000 Da, more preferably up to 2000 Da, and most preferably up to about 1000 Da.

Exemplary 5-HTR<sub>1D</sub> inhibitors that are contemplated by the present invention include, but are not limited to, those described in European patents EP0533268, EP0701819, EP0712397, EP0714389, EP0716650, EP0736023, EP0736025, EP0752982, EP0777650, EP0799226, EP0894085, EP1070065, EP1113015, EP1140931; European patent application EP1186318; US patents US5,356,893, US5,358,948, US5,436,246, US5,756,496, US5,801,170, US5,821,245, US5,919,932, US5,952,325, US5,972,935, US6,107,321, US6,107,328, US6,124,283, US6,159,962, US6,159,979, US6,166,034, US6,197,773, US6,342,498, US6,346,622, US6,355,647, US6,403,592, US6,509,340, US6,537,995, US6,887,905, US6,924,289, US7,026,314, US7,425,574, US7,432,282, US7,776,860, US9,938,277; US patent applications US20030064995, US20030212109, US20050085457, US20060009448, US20070010526; International patent applications WO1994015920, WO1995011243, WO1995030675, WO1999029666 and WO1999031086; the content of all of which is hereby incorporated by reference.

Typically, 5-HTR<sub>1D</sub> inhibitors which may be contemplated by the present invention include, but are not limited to:

- naphthalene derivatives, such as those described in EP0701819 and US5,821,245;
- tetrahydronaphthalene derivatives, such as those described in US6,124,283;
- carboxamide derivatives, such as those described in EP0712397, EP0752982 and US5,756,496;
- biphenylamide and biphenylethanone derivatives, such as those described in EP0736025, US5,801,170, US5,919,932, US5,972,935 and WO1995030675;
- benzanilide derivatives, such as those described in EP0533268, US5,356,893, US5,358,948, WO1994015920 and WO1995011243;
- *N*-acyl and *N*-aroyl aralkyl amides derivatives, such as those described in US6,197,773;
- indole, indoline, quinolone and quinoline derivatives, such as those described in EP0716650, EP0736023, EP0777650, US7,432,282, US20050085457, US20070010526, WO1999029666 and WO1999031086;

- tricyclic spiro derivatives, such as those described in US5,952,325;
- tetracyclic spiro derivatives, such as the one described in EP0799226;
- spiropiperidine derivatives, such as those described in US6,166,034;
- 2-pyrrolidones derivatives, such as those described in EP0894085, EP1113015  
5 and US6,924,289;
- 2,5-pyrrolidine-dione derivatives, such as those described in US6,537,995;
- heterocyclic lactam and imide derivatives, such as those described in  
US6,403,592;
- azabicyclic derivatives, such as those described in EP1070065, EP1140931 and  
10 US6,887,905;
- diazabicyclooctane derivatives, such as those described in US6,107,321;
- benzothiophene derivatives, such as those described in US5,436,246;
- benzisothiazole derivatives, such as those described in US6,346,622;
- benzofuranoxyethylamines derivatives, such as those described in US7,425,574;
- 15 - benzo[*b*]pyran derivatives, such as those described in US7,776,860;
- 1,4-thiazines derivatives, such as those described in US20060009448.
- arylpiperazine derivatives, such as those described in US6,342,498;
- 4-methylpiperazine derivatives, such as those described in EP0714389,  
US6,159,979 and US6,509,340;
- 20 - thieno[2,3-*d*]pyrimidine derivatives, such as those described in US6,159,962 and  
US6,355,647;
- piperazine and piperidine derivatives, such as the ones described in  
US20030064995;
- chromone derivatives, such as those described in US7,026,314; and
- 25 - ergoline derivatives, such as those described in US9,938,277.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0533268, including, without limitation, *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide; *N*-[4-chloro-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide; 2'-chloro-*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-

30

biphenyl]-4-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(1,2,3-thiadiazol-4-yl)[1,1'-biphenyl]-4-carboxamide; 2'-methyl-*N*-[4-methyl-3-(4-methyl-1-piperazinyl)phenyl]-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-carboxamide; 2-chloro-*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide; *N*-[4-chloro-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-carboxamide; *N*-[4-bromo-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)-2'-methyl-4'-(1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0701819, including, without limitation, 7-(imidazo[4,5-*b*]pyridin-1-yl)-1-(1-methylpyrrolidin-3-yl)naphthalene; 7-(4-chlorobenzamido)-1-(pyrrolidin-2-(*R*)-ylmethyl)naphthalene; 2-[8-(4-methylpiperazin-1-yl)naphthalen-2-yloxy]nicotinonitrile; 1-(4-methylpiperazin-1-yl)-7-pyrimidin-5-yl)naphthalene; 7-(5-cyanopyridin-3-yl)-1-(4-methylpiperazin-1-yl)naphthalene; 1-(piperazin-1-yl)-7-(pyrimidin-5-yl)naphthalene; 7-(4-chlorobenzamido)-1-(4-methylpiperazin-1-yl)naphthalene; 7-(3-methoxyphenyl)-1-(4-methylpiperazin-1-yl)naphthalene; 7-(imidazo[4,5-*b*]pyridin-1-yl)-1-(4-methylpiperazin-1-yl)naphthalene; 8-(4-methylpiperazin-1-yl)naphthalene-2-carboxylic acid 4-chlorobenzylamide; 7-(4-methoxyphenyl)-1-(4-methylpiperazin-1-yl)-naphthalene; 7-pyrimidin-2-yloxy-1-(4-methylpiperazin-1-yl)naphthalene; 7-(benzimidazol-1-yl)-1-(4-methylpiperazin-1-yl)naphthalene; 8-(1-methylpiperidin-4-yl)naphthalene-2-carboxylic acid 4-chlorobenzylamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0712397, including, without limitation, *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-2-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)furan-3-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(4-pyridyl)thiophene-2-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)pyridine-5-carboxamide; *N*-[4-methoxy-

3-(4-methyl-1-piperazinyl)phenyl]-2-(4-pyridyl)-3-methoxythiophene-4-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-5-(2-pyridyl)thiophene-2-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0714389, including, without limitation, *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-4-bromophenylacetamide; *N*-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-bromocinnamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-3-(thien-3-yl)acrylamide; *N*-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(4-pyridyl)cinnamide; *N*-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-phenylcinnamide; *N*-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-5-phenylpenta-2,4-dienamide; *N*-(4-bromophenyl)-*N*'-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; *N*-(4-bromo-3-methylphenyl)-*N*'-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; *N*-[3-methyl-4-(4-pyridyl)phenyl]-*N*'-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; *N*-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-4-(4-pyridyl)cinnamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0716650, including, without limitation, 1-[3-methyl-4-(4-pyridyl)benzoyl]-2,3-dihydro-5-methoxy-6-(4-methyl-1-piperazinyl)-1*H*-indole; 1-(4-bromo-3-methylbenzoyl)-2,3-dihydro-5-methoxy-6-(4-methyl-1-piperazinyl)-1*H*-indole; 1-(4-bromo-3-methylbenzoyl)-5-methoxy-6-(4-methyl-1-piperazinyl)-1*H*-indole; 2,3-dihydro-5-methoxy-6-(4-methyl-1-piperazinyl)-1-[2'-bromo-3'-methoxythiophene-4'-ylcarbonyl]indole; 2,3-dihydro-5-methoxy-6-(4-methyl-1-piperazinyl)-1-[4'-phenoxybenzoyl]indole; 2,3-dihydro-5-methoxy-1-[4-(2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)benzoyl]-6-(4-methyl-1-piperazinyl)-1*H*-indole; 5-methoxy-1-[4-(2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)benzoyl]-6-(4-methyl-1-piperazinyl)-1*H*-indole; 2,3-dihydro-5-methoxy-1-[4-(2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)benzoyl]-6-(1-piperazinyl)-1*H*-indole; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0736023, including, without limitation, 5-chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)benzoyl]1*H*-indole; 2,3-dihydro-6-(3-dimethylaminopropyl)-5-methoxy-1-[4-(2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)benzoyl]1*H*-indole; 2-3-dihydro-6-(2-(dimethylaminoethoxy)-5-methoxy-1-[4-2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)benzoyl]-1*H*-indole; 6-(2-(dimethylaminoethoxy)-5-methoxy-1-[4-(2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)benzoyl]-1*H*-indole; [7-(2-dimethylaminoethoxy)-6-methoxy-3,4-dihydro-2*H*-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone; [7-(3-dimethylaminopropyl)-6-methoxy-3,4-dihydro-2*H*-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0736025, including, without limitation, *N*-[7-[(2-dimethylaminoethyl)amino]-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[7-(2-dimethylamino)ethoxy-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[7-(3-dimethylaminopropyl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0752982, including, without limitation, *N*-[3-(2-dimethylaminoethoxy)4-methoxyphenyl]-4'-methoxycarbonyl-2'-methylbiphenyl-4-carboxamide; *N*-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-*N*-methylcarboxamidobiphenyl-4-carboxamide; *N*-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-*N,N*-dimethylcarboxamidobiphenyl-4-carboxamide; *N*-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-2'-methyl-4'-carboxamidobiphenyl-4-carboxamide; *N*-[3-(2-dimethylaminoethoxy)4-methoxyphenyl]-2'-methyl-4'-cyanobiphenyl-4-carboxamide; *N*-[3-(2-dimethylaminoethoxy)4-methoxyphenyl]-4'-acetyl-2'-methylbiphenyl-4-carboxamide; *N*-[3-(2-dimethylaminoethoxy)-4-

methoxyphenyl]-4'-[1-(methoxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide; *N*-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-4'-[1-(hydroxyimino)ethyl]-2'-methylbiphenyl-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0777650, including, without limitation, 1-(4'-acetamidomethyl-2'-methylbiphenyl-4-carbonyl)-5-chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1*H*-indole; 1-(4'-cyano-2'-methylbiphenyl-4-carbonyl)-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-methoxy-1*H*-indole; 1-(4'-acetyl-3'-methylbiphenyl-4-carbonyl)-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-methoxy-1*H*-indole; 1-(4'-acetyl-2'-methylbiphenyl-4-carbonyl)-6-(2-dimethylaminoethoxy)-5-methoxy-1*H*-indole; 1-(4'-acetyl-3'-methylbiphenyl-4-carbonyl)-6-(2-dimethylaminoethoxy)-5-methoxy-1*H*-indole; 1-(4'-cyano-2'-methylbiphenyl-4-carbonyl)-6-(2-dimethylaminoethoxy)-5-methoxy-1*H*-indole; 6-(2-dimethylaminoethoxy)-5-methoxy-1-(4'-(1-(methoxyimino)ethyl)-2'-methylbiphenyl-4-carbonyl)-1*H*-indole; 2,3-dihydro-6-(2-dimethylaminoethoxy)-5-methoxy-1-(5'-methoxy-carbonyl-2'-methylbiphenyl-4-carbonyl)-1*H*-indole; 6-(2-dimethylaminoethoxy)-5-methoxy-1-(2-methylbiphenyl-4-carbonyl)-1*H*-indole; 1-(4'-acetamidomethyl-2'-methylbiphenyl-4-carbonyl)-2,3-dihydro-6-(3-dimethylaminopropyl)-5-ethoxy-1*H*-indole; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0799226, including, without limitation, 1'-methyl-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-1'-methyl-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)spiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-ethyl-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f'*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-(5-dimethylamino-1,2,4-oxadiazol-3-yl)-2'-



methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-[4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 2,3-dihydro-1'-methyl-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)spiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-cyano-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-acetyl-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-(1-(methoxyamino)ethyl)-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-acetamidomethyl-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 3,5,6,7,8,9-hexahydro-1'-methyl-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)spiro[2*H*-furo[2,3-*h*]benzazepine-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(3-methyl-1,2,4-oxadiazol-5-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(5-ethyl-1,3,4-oxadiazol-2-yl)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 2,3-dihydro-1'-methyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)spiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(2,2'-dimethyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(2,3'-dimethyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(4-methylthiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-methoxycarbonyl-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(5'-methoxycarbonyl-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(methanesulphonamino)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-hydrazinocarbonyl-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-ethyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-

carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-5'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-carboxamido-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(4'-acetamido-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-1'-methyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)spiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-5-(4'-methanesulphonamino-2'-methylbiphenyl-4-carbonyl)-1'-methylspiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 1'-methyl-5-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrospiro[thiopheno[2,3-*f*]indole-3,4'-piperidine]; 1,2,3,5,6,7-hexahydro-1'-methyl-1-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)spiro[indeno[5,6-*b*]pyrrole-7,4'-piperidine]; 5-[4'-(*N*-methanesulphonyl-*N*-methylamino)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(dimethylaminosulphonyl)biphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(methanesulphonyl)biphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(*N,N*-dimethylcarbamoylamino)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(ethoxycarbonylamino)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(4,5-dimethyl-1,2,4-triazol-3-yl)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-6-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl]-2,3,7,8-tetrahydrospiro[4H-pyrano[2,3-*f*]indole-4,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(5-methyl-1,3,4-thiadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-1'-*N*-propyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(5-methyloxazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(3-methylisoxazol-5-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(5-methylisoxazol-3-yl)biphenyl-4-

- carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-1'-methyl-5-(4'-(5-dimethylamino-1,2,4-oxadiazol-3-yl)-2'-methylbiphenyl-4-carbonyl)spiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-1'-methyl-5-(4'-(5-ethyl-1,3,4-oxadiazol-2-yl)-2'-methylbiphenyl-4-
- 5 carbonyl)spiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-1'-methyl-5-(4'-methoxycarbonyl-2'-methylbiphenyl-4-carbonyl)spiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-1'-methyl-5-(4'-hydrazinocarbonyl-2'-methylbiphenyl-4-carbonyl)spiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 2,3,5,6,7,8-hexahydro-1'-methyl-5-(2'-methyl-4'-(1,3,4-oxadiazol-2-yl)biphenyl-4-
- 10 carbonyl)spiro[furo[2,3-*g*]quinoline-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-pyrazinylbiphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazolyl-3-yl)biphenyl-4-carbonyl]-1-oxo-2,3,6,7-tetrahydrospiro[thiopheno[2,3-*f*]indole-3,4'-piperidine]; 1'-ethyl-5-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl]-2,3,6,7-
- 15 tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-[2'-methyl-4'-(1-methylimidazol-2-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-[2'-methyl-4'-(1-methylimidazol-5-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(5-hydroxymethyl-1,2,4-oxadiazol-3-yl)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-
- 20 tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-1'-oxo-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-methyl-5-[2'-methyl-4'-(1,2,4-triazin-3-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 2,3,6,7,8,9-hexahydro-1'-methyl-6-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-
- 25 carbonyl)spiro[4*H*-pyrano[2,3-*g*]quinoline-4,4' piperidine]; 1'-ethyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-1'-oxo-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-ethyl-5-[4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 1'-ethyl-5-(4'-hydrazinocarbonyl-2'-methylbiphenyl-4-carbonyl)-2,3,6,7-
- 30 tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(acetylhydrazinocarbonyl)-2'-methylbiphenyl-4-carbonyl]-1'-ethyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]; 5-[4'-(5-methoxymethyl-1,2,4-oxadiazol-3-yl)-2'-methylbiphenyl-4-

carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]; 5-[4'-(4,5-dihydrooxazol-2-yl)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]; 5-[4'-(2-(*N,N*-dimethylamino)acetamido)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]; 5-[4'-(ethoxycarbonylamino)-2'-methylbiphenyl-4-carbonyl]-1'-ethyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]; 5-[4'-(acetylhydrazinocarbonyl)-2'-methylbiphenyl-4-carbonyl]-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]; 5-(4'-(5-methylfuran-2-yl)-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP0894085, including, without limitation, 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 6-chloro-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 5-chloro-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 1-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-phenyl-1,3-dihydro-indol-2-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-dichlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 1-(4-chlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(4-chlorobenzyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-difluorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(2,4-dichlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(4-chlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(3,4-dichlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(4-chlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(3,4-dichlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-phenyl-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-(4-trifluoromethylphenyl)-pyrrolidin-2-one; 1-(3,4-difluorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 3-[2-(4-

methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzyl]-piperidin-2-one; 1-(3,4-dichlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzyl]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzyl]-1-phenyl-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-(p-tolyl)-pyrrolidin-2-one; 3-[4-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-1-phenyl-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-fluoro-6-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-difluorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidine-2-one; 1-[2-(4-chlorophenyl)ethyl]-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)benzyl]-1-(4-trifluoromethylphenyl)-pyrrolidin-2-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in EP1070065, including, without limitation, (7*R*,9*aS*)-*trans*-1-{3-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-benzyl}-azetidin-3-ol; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-morpholin-4-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-1-[3-(2-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-azetidin-3-ol; (7*R*,9*aS*)-*trans*-2-(4-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-1-[3-(2-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]pyrrolidine-3,4-diol; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydropyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(2-methyl-5-pyrimidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(3-methoxy-5-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(4-chloro-3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(4-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-7-(3-azetidin-1-ylmethyl-phenoxy-methyl)-2-

benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-cyclopropylmethyl-amine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[3-(2-methoxymethyl-pyrrolidin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-cyclopropyl-amine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[3-(4-ethyl-piperazin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-cyclohexyl-amine; (7*S*,9*aS*)-*cis*-1-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-pyrrolidin-3-ol; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[3-(2,5-dimethyl-[pyrrolidin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-isobutyl-amine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(2-morpholin-4-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(2-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(4-morpholin-4-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(7-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(6-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(6,7-difluoro-benzodisoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-3-{3-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-benzyl}-3-aza-bicyclo[3.2.2]nonane; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-*cis*-octahydro-isoindol-2-ylmethyl]-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-4-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido-1,2-*a*]pyrazin-7-ylmethoxy)-benzylamine; (7*S*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(2-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-chloro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-methyl-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl)-7-(2-

pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl)-7-(2-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(2-morpholin-4-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(4-morpholin-4-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(2-methoxy-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-(5-methoxy-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethylphenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-(2-methoxymethylpyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-(2-methoxymethylpyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-(2-methoxymethylpiperidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-(3-methoxymethylpiperidin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR1D inhibitor according to the present invention is selected from those described in EP1113015, including, without limitation, (-)-3(*S*)-[[2-(4-methyl-1-piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-pyrrolidinone; (+)-3(*R*)-[[2-(4-methyl-1-piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-pyrrolidinone; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR1D inhibitor according to the present invention is selected from those described in EP1140931, including, without limitation, (7*R*,9*aS*)-*trans*-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-methyl-pyrimidin-2-yl)-amine; (7*S*,9*aS*)-*cis*-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-methyl-pyrimidin-2-yl)-amine; (7*R*,9*aS*)-*trans*-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-chloro-pyrimidin-2-yl)-amine; (7*S*,9*aS*)-*cis*-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-5-chloro-pyrimidin-2-yl)-amine; (7*R*,9*aS*)-*trans*-(5-chloro-

pyrimidin-2-yl)-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-amine; (7*S*,9*aS*)-*cis*-(5-chloro-pyrimidin-2-yl)-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-amine; (7*R*,9*aS*)-*trans*-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-(5-methyl-pyrimidin-2-yl)amine; (7*S*,9*aS*)-*cis*-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-(5-methyl-pyrimidin-2-yl)amine; (7*R*,9*aS*)-*trans*-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-fluoro-pyridin-2-yl)-amine; (7*S*,9*aS*)-*cis*-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-fluoro-pyridin-2-yl)-amine; (7*R*,9*aS*)-*trans*-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-(5-fluoro-pyridin-2-yl)-amine; (7*S*,9*aS*)-*cis*-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-(5-fluoro-pyridin-2-yl)-amine; (7*R*,9*aS*)-*trans*-(2-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-fluoro-3-methyl-pyridin-2-yl)-amine; (7*S*,9*aS*)-*cis*-(2-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-fluoro-3-methyl-pyridin-2-yl)-amine; (7*R*,9*aS*)-*trans*-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-(5-fluoro-3-methyl-pyridin-2-yl)-amine; (7*S*,9*aS*)-*cis*-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl]-(5-fluoro-3-methyl-pyridin-2-yl)-amine; (7*R*,9*aS*)-*trans*-(2-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethyl)-(5-fluoro-pyrimidin-2-yl)-amine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR1D inhibitor according to the present invention is selected from those described in EP1186318, including, without limitation, 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-imidazolidine-2,4-dione; 3-(4-chlorobenzyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-imidazolidine-2,4-dione; 3-(4-chlorobenzyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 4-benzyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorobenzyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 3-(4-trifluoromethylphenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one;



4-(3,4-dichlorophenyl)-2-[2-fluoro-6-(4-methylpiperazin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-  
 benzylidene]-morpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-  
 benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-  
 5 yl)-benzyl]-thiomorpholin-3-one; 4-methyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(2-piperazin-1-ylbenzylidene)-  
 thiomorpholin-3-one; 4-benzyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,1-  
 dioxothiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[3-fluoro-2-(4-methylpiperazin-1-  
 yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-fluoro-2-(4-  
 10 methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-1-[2-  
 (4-methylpiperazin-1-yl)-5-trifluoromethyl-benzylidene]-thiomorpholin-3-one; 4-(3,4-  
 dichlorophenyl)-2-{2-[4-(2-methoxyethyl)piperazin-1-yl]-benzylidene}-thiomorpholin-  
 3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-isopropylpiperazin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-ethylpiperazin-1-yl)-benzylidene]-  
 15 thiomorpholin-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 4-(3-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 2-[2-chloro-6-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-  
 dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-  
 1-yl)-4-trifluoromethyl-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-  
 20 (4-methylpiperazin-1-yl)-benzylidene]-1-oxo-thiomorpholin-3-one; 4-(3,4-  
 dichlorophenyl)-2-(5-fluoro-2-piperazin-1-yl-benzylidene)-thiomorpholin 3-one; 4-(3,4-  
 dichlorophenyl)-2-[3,6-difluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-  
 benzylidene]-thiomorpholin-3-one; 4-phenyl-2-[2-(3,4,5-trimethylpiperazin-1-yl)-  
 25 benzylidene]-thiomorpholin-3-one; 2-[5-fluoro-2-(4-methylpiperazin-1-yl)-  
 benzylidene]-4-phenyl-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(3,5-  
 dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-tert-butylpiperazin-  
 1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 3-(3,4-  
 dichlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidin 4-one; 3-[4-  
 30 (3,4-dichlorophenyl)-3-oxo-thiomorpholin-2-ylidenemethyl]-6-dimethylamino 2-(4-  
 methylpiperazin-1-yl)-benzonitrile; 5-[2-(4-methylpiperazin-1-yl)-benzylidene]-2-  
 phenylthiazolidin-4-one; 4-(3,4-dichlorophenyl)-2-[2-(3,4,5-trimethylpiperazin-1-yl)-

benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-methyl-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[4-chloro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one;

5 one; 4-(2,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[4-bromo-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-

10 [2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(octahydropyrido[1,2-*a*]pyrazin-2-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-pyridin-3-yl-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-difluorophenyl)-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-

15 4-(3,5-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-methylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one;

20 one; 4-(3,4-difluorophenyl)-2-[2-(2,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-4-(4-fluorophenyl)-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-4-phenylthiomorpholin-3-one; 4-(3,4-

25 dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one;

30 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-[1,4]diazepan-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(2,4,6-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 2-[2,4-dibromo-6-

(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4]oxazepan-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4,5]oxadiazepan-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4]thiazepan-3-one; 4-  
 5 (3,4-dichlorophenyl)-2-{2-[(2-dimethylaminoethyl)-methyl-amino]-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpiperidin-4-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1,4-dimethylpiperidin-4-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholine-3,5-dione; 4-(3,4-dichlorophenyl)-  
 10 2-[2-(2-dimethylaminoethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-isopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpyrrolidin-3-ylmethyl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-[methyl-(1-methylpyrrolidin-2-ylmethyl)-amino]-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-[2-(1-methylpyrrolidin-2-yl)-ethyl]-benzylidene}-thiomorpholin-3-one; 1-(3,4-dichlorophenyl)-4-methyl-3-(2-(4-methylpiperazin-1-yl)-benzylidene)-piperazin-2-one; 4-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-(4-trifluoromethylphenyl)-piperazin-2-one; 1-(4-chlorophenyl)-4-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperazin-2-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-morpholin-3-one; 2-[4-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-{1-[2-(4-methylpiperazin-1-yl)-phenyl]-ethylidene}-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzyl]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 4-(4-chlorophenyl)-6-methyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 3-(4-chlorophenyl)-2,2-dimethyl-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidin-4-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4]oxazepan-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4*H*-[1,4]thiazin-3-one; 1-(4-chlorophenyl)-4,6,6-trimethyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperazin-2-one; 1-(4-chlorophenyl)-4-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-

- piperazin-2-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-  
 morpholin-3-one; 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-  
 oxazolidin-4-one; 3-(4-chlorophenyl)-2,2-dimethyl-5-[2-(4-methylpiperazin-1-yl)-  
 benzylidene]-imidazolidin-4-one; 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-  
 5 benzylidene]-imidazolidin-4-one; 5-[2-(4-methylpiperazin-1-yl)-phenyl]-furan-2-  
 carboxylic acid 4-chlorobenzylamide; 5-[2-(4-methylpiperazin-1-yl)-phenyl]-furan-2-  
 carboxylic acid 4-chlorophenylamide; 5-[2-(4-methylpiperazin-1-yl)-phenyl]-thiophene-  
 2-carboxylic acid 4-chlorophenylamide; 5-[2-(4-methylpiperazin-1-yl)-phenyl]-furan-2-  
 carboxylic acid [2-(4-chlorophenyl)ethyl]-amide; 4-[2-(4-methylpiperazin-1-yl)-  
 10 phenyl]-furan-2-carboxylic acid 4-chlorobenzylamide; 5-[2-(4-methylpiperazin-1-yl)-  
 phenyl]-thiophene-2-carboxylic acid benzylamide; 5-[2-(4-methylpiperazin-1-yl)-  
 phenyl]-thiophene-2-carboxylic acid 4-fluorobenzylamide; 5-[2-(4-methylpiperazin-1-  
 yl)-phenyl]-thiophene-2-carboxylic acid 4-methoxybenzylamide; 5-[2-(4-  
 methylpiperazin-1-yl-phenyl]-thiophene-2-carboxylic acid [2-(4-chlorophenyl)ethyl]-  
 15 amide; 3-methyl-5-[2-(4-methylpiperazin-1-yl)-phenyl]-thiophene-2-carboxylic acid 4-  
 chlorobenzylamide; 5-[5-fluoro-2-(4-methylpiperazin-1-yl)-phenyl]-thiophene-2-  
 carboxylic acid 4-chlorobenzylamide; 5-(2-(4-methylpiperazin-1-yl)-phenyl)-1*H*-  
 pyrrole-2-carboxylic acid 4-chlorobenzylamide; and pharmaceutically acceptable salts or  
 esters thereof.
- 20 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected  
 from those described in US5,356,893, including, without limitation, *N*-4-methoxy-3-(4-  
 methyl-1-piperazinyl)phenyl-2-methyl-4'-(methylsulphinyl)-1,1'-biphenyl-4-  
 carboxamide; 4'-acetyl-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2-methyl-1,1'-  
 biphenyl-4-carboxamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-4'-  
 25 methylamino-1,1'-biphenyl-4-carboxamide; methyl-4'-4-methoxy-3-(4-methyl-1-  
 piperazinyl)phenylaminocarbonyl-2-methyl-(1,1'-biphenyl-4-yl)methyl carbamate; 4'-4-  
 methoxy-3-(4-methyl-1-piperazinyl)phenylaminocarbonyl-2'-methyl-1,1'-biphenyl-4-  
 dimethylcarbamate; 4'-(methoxyacetyl)methylaminomethyl-*N*-4-methoxy-3-(4-methyl-  
 1-piperazinyl)phenyl-2'-methyl-1,1'-biphenyl-4-carboxamide; 4'-acetyl-2'-  
 30 trifluoromethyl-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-1,1'-biphenyl-4-  
 carboxamide; *N*-4-bromo-3-(4-methyl-1-piperazinyl)phenyl-*N*',*N*',2'-trimethyl-1,1'-

biphenyl-4,4'-dicarboxamide; 4'-hydroxy-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-1,1'-biphenyl-4-carboxamide; 4'-acetyl-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-1,1'-biphenyl-4-carboxamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-4'-(4-morpholinylcarbonyl)-1,1'-biphenyl-4-carboxamide; 4'-acetyl-2'-methoxy-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-1,1'-biphenyl-4-carboxamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-*N'*,*N'*-dimethyl-1,1'-biphenyl-4,4'-dicarboxamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-4'-(1-pyrrolidinyl)carbonyl-1,1'-biphenyl-4-carboxamide; *N,N*-diethyl-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2-methyl-1,1'-biphenyl-4,4'-dicarboxamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-4'-(methylsulphonyl)amino-1,1'-biphenyl-4-carboxamide; *N*-butyl-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-*N'*,*N'*-2-dimethyl-1,1'-biphenyl-4,4'-dicarboxamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-*N'*,*N'*-dipropyl-1,1'-biphenyl-4,4'-dicarboxamide; 4'-(2-methoxyethoxy)methyl-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-1,1'-biphenyl-4-carboxamide; 4'-cyano-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-1,1'-biphenyl-4-carboxamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-*N'*,*N'*,2'-trimethyl-1,1'-biphenyl-4,4'-dicarboxamide; 4'-(dimethylamino)-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-1,1'-biphenyl-4-carboxamide; 2-chloro-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-*N,N*-dimethyl-1,1'-biphenyl-4,4'-dicarboxamide; *N*-4-chloro-3-(4-methyl-1-piperazinyl)phenyl-*N'*,*N'*,2'-trimethyl-1,1'-biphenyl-4,4'-dicarboxamide; *N*-(1,1-dimethylethyl)-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2-methyl-1,1'-biphenyl-4,4'-dicarboxamide; 4'-(1-azetidyl)carbonyl-*N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2'-methyl-1,1'-biphenyl-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US5,358,948, including, without limitation, *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-4-(4-pyridinyl)benzamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-4-(4-methyl-3-pyridinyl)benzamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-3-methyl-4-(4-pyridinyl)benzamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-2-methyl-4-(4-pyridinyl)benzamide; *N*-4-methyl-3-(4-methyl-1-

piperazinyl)phenyl-4-(4-pyridinyl)benzamide; *N*-4-chloro-3-(4-methyl-1-  
 piperazinyl)phenyl-4-(4-pyridinyl)benzamide; *N*-4-fluoro-3-(4-methyl-1-  
 piperazinyl)phenyl-4-(4-pyridinyl)benzamide; *N*-4-methoxy-3-(4-methyl-1-piperazinyl-  
 4-(3-methyl-4-pyridinyl)benzamide; *N*-6-fluoro-4-methoxy-3-(4-methyl-1-  
 5 piperazinyl)phenyl-3-methyl-4-(4-pyridinyl)benzamide; *N*-4-bromo-3-(4-methyl-1-  
 piperazinyl)phenyl-3-methyl-4-(4-pyridinyl)benzamide; *N*-3-(4-methyl-1-  
 piperazinyl)phenyl-4-(4-pyridinyl)benzamide; 4-(4-pyridinyl)-2-methoxy-*N*-4-methoxy-  
 3-(4-methyl-1-piperazinyl)phenylbenzamide; *N*-4-hydroxy-3-(4-methyl-1-  
 piperazinyl)phenyl-4-(4-pyridinyl) benzamide; and pharmaceutically acceptable salts or  
 10 esters thereof.

In one embodiment, the 5-HT<sub>1D</sub> inhibitor according to the present invention is selected  
 from those described in US5,436,246, including, without limitation, 4-4-(2-phenylethyl)-  
 1-piperazinyl-benzo[*b*]thiophene-2-methanol monohydrochloride; 4-4-(2-phenylethyl)-  
 1-piperazinyl-benzo[*b*]thiophene-2-carboxamide; 4-4-(2-phenylethyl)-1-piperazinyl-  
 15 benzo[*b*]thiophene-2-nitrile; 4-4-(3-phenylpropyl)-1-piperazinyl-benzo[*b*]thiophene-2-  
 methanol; 4-4-(3-phenylpropyl)-1-piperazinyl-benzo[*b*]thiophene-2-carboxamide; 4-4-  
 2-(4-methoxyphenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-methanol; 4-4-2-(4-  
 chlorophenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-carboxamide; 4-4-2-(4-  
 chlorophenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-methanol; 4-4-2-(4-  
 20 methylphenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-methanol; 4-4-(2-phenylethyl)-  
 1-piperazinyl-benzo[*b*]thiophene-2-(*N*-methyl)-carboxamide; 4-4-(2-phenylethyl)-1-  
 piperazinyl-benzo[*b*]thiophene-2-(*N,N*-dimethyl)-carboxamide; 4-4-2-(4-  
 methylphenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-carboxamide; 4-4-2-(4-  
 fluorophenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-methanol; 4-4-2-(4-  
 25 fluorophenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-carboxamide; 4-(4-propyl)-1-  
 piperazinylbenzo[*b*]thiophene-2-carboxylate hydrochloride; 4-(4-propyl)-1-  
 piperazinylbenzo[*b*]thiophene-2-methanol hydrochloride; 4-4-(2-phenylethyl)-1-  
 piperazinyl-benzo[*b*]thiophene-2-(*N*-ethyl)carboxamide hydrochloride; 4-4-(2-  
 phenylethyl)-1-piperazinyl-benzo[*b*]thiophene-2-(*O*-methyl)-methanol hydrochloride; 4-  
 30 4-propyl-1-piperazinyl-benzo[*b*]thiophene-2-*N*-methylcarboxamide hydrochloride; 4-4-  
 methyl-1-piperazinyl-benzo[*b*]thiophene-2-methanol hydrochloride; 4-4-(2-

phenylethyl)-1-piperazinyl-benzo[*b*]thiophene-2-(*N*-methyl-*N*-methoxy)-carboxamide hydrochloride; 2-4-4-(2-phenylethyl)-1-piperazinylbenzo[*b*]thiophene-2-(2-propanol) hydrochloride; 1-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-ethanone hydrochloride; 1-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-ethanol hydrochloride; 4-4-phenylmethyl-1-piperazinyl-benzo[*b*]thiophene-2-methoxymethyl hydrochloride; 4-(1-piperazinyl)-benzo[*b*]thiophene-2-methoxymethyl hydrochloride; 4-4-(2-(4-fluorophenyl)-ethyl)-1-piperazinylbenzo[*b*]thiophene-2-methoxymethyl hydrochloride; 4-4-(2-phenylethyl)-1-piperazinyl-benzo[*b*]thiophene-2-carboxaldehyde; 4-4-(4-phenylcarbomoyl-butyl)-piperazin-1-yl-benzo[*b*]thiophen-2-carboxylic acid ethyl ester hydrochloride; 4-(1-piperazinyl)benzo[*b*]thiophene-2-(*N*-methyl)carboxamide; 4-4-2-(4-nitrophenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-methanol hydrochloride dihydrochloride; 4-(1-piperazinyl)benzo[*b*]thiophene-2-methanol hydrochloride; 4-4-2-(4-nitrophenyl)ethyl-1-piperazinyl-benzo[*b*]thiophene-2-carboxylate hydrochloride; 5-4-(2-hydroxymethyl-benzo[*b*]thiophen-4-yl)-piperazin-1-yl)-pentanoic acid phenyl amide hydrochloride; 2-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-ylmethyl-isoindole-1,3-dione hydrochloride; 4-4-(2-phenylethyl)-1-piperazinyl-benzo[*b*]thiophene-2-methanamine dihydrochloride; 4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-piperidin-1-yl methanone hydrochloride; 4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-ylpyrrolidin-1-yl methanone hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-acrylic acid ethyl ester hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-prop-2-en-1-ol hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-acrylonitrile hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-acrylamide hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-propionic acid ethyl ester hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-propan-1-ol hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-propionitrile hydrochloride; 3-4-(4-phenethyl-piperazin-1-yl)-benzo[*b*]thiophen-2-yl-propionamide hydrochloride; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US5,756,496, including, without limitation, *N*-1-(2-

dimethylaminoethyl)-1*H*-indol-6-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-2,3-dihydro-1-(2-dimethylaminoethyl)-1*H*-indol-6-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-4-(2-dimethylaminoethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethyl)-1*H*-indol-5-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-4-(2-dimethylaminoethyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin-6-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-4-(2-dimethylaminoethyl)-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazin-6-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-4-(2-dimethylaminoethyl)-3,4-dihydro-2*H*-benzo[*b*]pyran-6-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethyl)-2-oxo-2(3*H*)-benzoxazol-5-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-5-(2-dimethylaminoethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepin-7-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR1D inhibitor according to the present invention is selected from those described in US5,801,170, including, without limitation, *N*-3-(dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-diethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-diisopropylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylamino-1-methylethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminopropoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-Methylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-Aminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-piperidin-1-ylethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-morpholin-4-ylethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(3-methyl-1,2,4-



oxadiazol-5-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carboxamide;  
*N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(1,3,4-oxadiazol-2-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)phenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-5-(2-dimethylaminoethoxy)-2,4-diiodophenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethyl)amino-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-carboxamide; *N*-3-(3-dimethylaminopropoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(3-dimethylaminopropyl)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(3-dimethylaminoprop-1-enyl)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-4-(3-dimethylaminopropoxy)phenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-pyrrolidin-1-ylethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-ethyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(5-dimethylamino-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-(4-methylthiazol-2-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-methyl-4'-pyrazinyl biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethylthio)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethylsulphinyl)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-5-(2-dimethylaminoethoxy)-2-chlorophenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-chlorophenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-bromophenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-iodophenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-ethylphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-isopropylphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-

yl)biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-4'-(1,2,4-triazol-1-yl)-2'-methyl-(1,1'-biphenyl)-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-4'-(1,2,4-triazol-1-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-4'-(tetrazol-2-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2-methyl-4'-(2-pyridyl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2-methyl-4'-(3-pyridyl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2'-ethyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenyl-2,2'-dimethyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(*N'*-(2-dimethylaminoethyl)-*N'*-methylamino)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(*N'*-(2-dimethylaminoethoxy)-*N'*-phenethylamino)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(*N'*-(2-dimethylaminoethoxy)-*N'*-butylamino)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenol-4'-(1,2,4-triazol-1-yl)-(1,1'-biphenyl)-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenol-4'-(tetrazol-2-yl)-(1,1'-biphenyl)-4-carboxamide; *N*-3-(2-dimethylaminoethoxy)-4-methoxyphenol-2'-methyl-4'-(1,2,4-triazol-1-yl)-(1,1'-biphenyl)-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US5,821,245, including, without limitation, 7-benzamido-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(1-naphthylcarboxamido)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-benzamido-1-(1-piperazinyl)-naphthalene; 7-acetamido-1-(4-methyl-1-piperazinyl)-naphthalene; 7-hexanamido-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(phenylaminocarbonylamino)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(benzyloxycarbonylamino)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(3-nitro-2-pyridinylamino)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(5-nitro-2-pyridylamino)-1-

(4-methyl-1-piperazinyl)-naphthalene; 7-(3-hydroxy-3-methyl-1-butynyl)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(2-ethylsulfonyl)ethenyl-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(3-methylaminosulfonylphenyl)-1-(4-methyl-1-piperazinyl)naphthalene; 7-benzoyl-1-(4-methyl-1-piperazinyl)naphthalene; 7-(3-methoxycarbonylphenyl)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(3-fluorophenyl)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(benzyloxy)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(4-chlorobenzoyloxy)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(imidazole[4,5-*b*]pyridin-1-yl)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(benzimidazol-1-yl)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(5-cyanobenzimidazol-1-yl)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(5-trifluoromethylbenzimidazol-1-yl)-1-(4-methyl-1-piperazinyl)-naphthalene; 7-(6,7-dichlorobenzimidazol-1-yl)-1-(4-methyl-1-piperazinyl)-naphthalene; 2-8-(4-methylpiperazin-1-yl)naphthalen-2-yloxymethylquinoline; 1-methyl-4-{7-2-(4-chlorophenyl)thiazol-5-ylmethoxynaphthalen-1-yl}piperazine; 1-methyl-4-7-(5-chloro-thiophen-2-ylmethoxy)naphthalen-1-ylpiperazine; 8-(4-methylpiperazin-1-yl)naphthalene-2-carboxylic acid phenylamide; 7-amino-1-(1-methyl-4-piperidiny)-naphthalene; 7-(3-nitro-2-pyridylamino)-1-(1-methyl-4-piperidiny)-naphthalene; 7-(imidazolo[4,5-*b*]pyridin-1-yl)-1-(1-methyl-4-piperidiny)-naphthalene; 7-(4-chlorobenzamido-1-(1-methyl-4-piperidiny)-naphthalene; 7-amino-1-(1-methyl-3-piperidiny)-naphthalene; 7-(3-nitro-2-pyridylamino)-1-(1-methyl-3-piperidiny)-naphthalene; 7-(imidazole[4,5-*b*]pyridin-1-yl)-1-(1-methyl-3-piperidiny)-naphthalene; 7-benzamido-1-(1-methyl-3-piperidiny)-naphthalene; 7-(4-chlorobenzamido)-1-(4-methoxyethyl-1-piperazinyl)-naphthalene; 7-(4-chlorobenzamido)-1-(4-propyl-1-piperazinyl)-naphthalene; 7-(4-chlorobenzamido)-1-(4-ethyl-1-piperazinyl)-naphthalene; 7-amino-1-(1-piperazinyl)-naphthalene; 7-(imidazolo-[4,5-*b*]pyridin-1-yl)-1-(1-piperazinyl)-naphthalene; 7-(1,2,3-triazolo-4,5-*b*-pyridin-1-yl)-1-(1-piperazinyl)-naphthalene; 1-{7-5-(2-methoxyphenyl)-1,2,4-oxadiazol-3-ylmethoxy-naphthalen-1-yl}-4-methylpiperazine; 1-7-(5-tert-butyl-1,2,4-oxadiazol-3-ylmethoxy)-naphthalen-1-yl-4-methylpiperazine; 1-methyl-4-7-(3-phenyl-1,2,4-oxadiazol-5-ylmethoxy)-naphthalen-1-yl-piperazine; 1-methyl-4-7-(5-phenyl-1,2,4-oxadiazol-3-ylmethoxy)-naphthalen-1-yl-piperazine; 1-{7-5-(3-methoxyphenyl)-1,2,4-oxadiazol-3-ylmethoxy-naphthalen-1-yl}-4-methylpiperazine; 1-{7-5-(3,5-dimethylisoxazol-4-yl)-1,2,4-oxadiazol-3-ylmethoxy-naphthalen-1-yl}-4-

methylpiperazine; 1-{7-3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ylmethoxy-naphthalen-1-yl}-4-methylpiperazine; 2-8-(1-methylpiperidin-4-yl)-naphthalen-2-yloxy-pyrimidine; 1-methyl-4-7-(3-pyridin-3-ylmethyl-1,2,4-oxadiazol-5-yl)-naphthalen-1-yl-piperazine; 1-methyl-4-7-(pyridin-2-ylmethoxy)-naphthalen-1-yl-piperazine; 7-(imidazole[4,5-*b*]pyridin-1-yl)-1-(1-methylpyrrolidin-3-yl)naphthalene; 2-8-(4-methylpiperazin-1-yl)naphthalen-2-yloxynicotinonitrile; 1-(4-methylpiperazin-1-yl)-7-pyrimidin-5-yl)naphthalene; 7-(4-chlorobenzamido-1-(4-methylpiperazin-1-yl)naphthalene; 7-(3-methoxyphenyl)1-(4-methylpiperazin-1-yl)naphthalene; 8-(4-methylpiperazin-1-yl)naphthalene-2-carboxylic acid 4-chlorobenzylamide; 7-pyrimidin-2-yloxy-1-(4-methylpiperazin-1-yl)naphthalene; 7-(4-methoxyphenyl)-1-(4-methylpiperazin-1-yl)-naphthalene; 8-(1-methylpiperidin-4-yl)naphthalene-2-carboxylic acid 4-chlorobenzylamide; 1-{7-3-(4-chloro-benzyl)-1,2,4-oxadiazol-5-yl-naphthalen-1-yl}-4-methyl-piperazine; 4-{7-3-(4-chloro-benzyl)-1,2,4-oxadiazol-5-yl-naphthalen-1-yl}-1-methyl-piperidine; 7-(3-methoxyphenyl)-1-(1-methylpiperidin-4-yl)-naphthalene; 7-(4-methoxyphenyl)-1-(1-methylpiperidin-4-yl)-naphthalene; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US5,919,932, including, without limitation, *N*-3-(8-azabicyclo-3.2.1-octan-3-yl)-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-4-methoxy-3-(8-methyl-8-azabicyclo-3.2.1-octan-3-yl)phenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; 3,4-dihydro-6-methoxy-7-(8-methyl-8-azabicyclo-3.2.1-octan-3-yl)-2*H*-quinolin-1-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-ylmethanone; 7-(8-azabicyclo3.2.1 octan-3-yl)-3,4-dihydro-6-methoxy-2*H*-quinolin-1-yl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-ylmethanone; *N*-3-(8-methyl-8-azabicyclo3.2.1 octan-3-yl)phenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US5,952,325, including, without limitation, *N*-(2,3-dihydro-1'-methylspiro-4*H*-benzopyran-6-yl-4,4'-piperidine)-2'-methyl-4'-(5-methyl-1,2,4-

oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-(2,3-dihydrospiro-4*H*-benzopyran-6-yl-4,4'-piperidine)-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-(2,3-dihydro-1'-methylspirobenzofuran-5-yl-3,4'-piperidine)-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-(2,3-dihydro-1'-methylspirobenzothiophen-5-yl-3,4'-piperidine)-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-5-yl)biphenyl-4-carboxamide; *N*-(1,2,3,5,6,7-hexahydro-1-methylspiro-4*H*-azepine-4,3'(2*H*)-benzofuran-5'-yl)-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US5,972,935, including, without limitation, 4-(2-dimethylaminoethyl)-2,3,6,7,8,9-hexahydro-6-{2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl}-4*H*-pyrido[2,3-*g*][1,4]benzoxazine; 2-(*N,N*-dimethyl-3,4,6,7,8,9-hexahydro-6-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-2*H*-pyrano[2,3-*g*]quinolin-4-yl)ethanamine; 2-(*N,N*-dimethyl-2,3,5,6,7,8-hexahydro-5-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]furo[2,3-*g*]quinolin-3-yl)ethanamine; 4-(2-dimethylaminoethyl)-2,3,4,6,7,8-hexahydro-6-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]pyrrolo[2,3-*g*][1,4]benzoxazine; 3-(2-dimethylaminoethyl)-5-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-2,3,6,7-tetrahydrofuro[2,3-*f*]indole; 4-(2-dimethylaminoethyl)-2,3,6,7,8,9-hexahydro-6-[2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl]-4*H*-pyrido[2,3-*g*][1,4]benzoxazine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,107,321, including, without limitation, 3-benzyl-7-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-*s*-3,7-diazabicyclo[3.3.0]octane; 3-(pyridin-3-yl)methyl-7-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-*cis*-3,7-diazabicyclo[3.3.0]octane; 3-[2-(4-(acetylamino)phenyl)ethyl]-7-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-*cis*-3,7-diazabicyclo[3.3.0]octane; 3-benzoyl-7-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-*cis*-3,7-diazabicyclo[3.3.0]octane; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,107,328, including, without limitation, 4-(hydroxymethyl)-1-methyl-1,2,3,6-tetrahydropyridine; 4-(2-iodophenoxymethyl)-1-methyl-1,2,3,6-tetrahydropyridine; 2,3-dihydro-1'-methylspirobenzofuran-3,4'-piperidine; 2,3-dihydro-1'-methyl-5-nitrospirobenzofuran-3,4'-piperidine; 5-amino-2,3-dihydro-1'-methylspirobenzofuran-3,4'-piperidine; 6-(cyanomethyl)-2,3-dihydro-1'-methyl-5-nitrospirobenzofuran-3,4'-piperidine; 2,3-dihydro-1'-methylspirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,124,283, including, without limitation, (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(trifluoroacetyl)benzamide; (*R*)-*N*-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-piperidinobenzamide; (*S*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-*N,N*-diethylaminobenzamide; (*R*)-*N*-8-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-ethylbenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinocarbonylbenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-butoxybenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(1*H*-pyrrol-1-yl)benzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-3-methyl-4-morpholinobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(4-ethylphenyl)benzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-trifluoromethylbenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(*N,N*-dipropylaminosulphonyl)benzamide; (*R*)-*N*-8-(4-ethylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-8-(1-

methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-trifluoromethylbenzamide; (*R*)-*N*-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-butoxybenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-cyclohexylbenzamide; (*R*)-*N*-8-(methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(4-piperidon-1-yl)benzamide; (*R*)-*N*-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; *N*-(4-morpholinocarbonylphenyl)-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(4-morpholinomethyl)benzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(*N,N*-dimethylaminocarbonyl)benzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinocarbonylbenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-thiomorpholinobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-2-methylbenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-cyanobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-fluorobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(4-hydroxyphenyl)benzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-3-phenoxybenzamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,159,962, including, without limitation, 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxy-phenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methyl-1-naphthyl)-1-piperazinyl)ethylthieno-[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxy-1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methylphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(3-trifluoromethylphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-chloro-phenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-pyrimidin-2-

ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-pyridin-2-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-quinolin-2-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(3,5-dichlorophenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-tetralin-5-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-indan-4-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-cyanophenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-isoquinolin-4-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxyphenyl)-1-piperidinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxyphenyl)-3,4-dihydro-1-piperidinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-naphth-1-ylpiperidin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxy-1-naphthyl)-3,4-dehydro-1-piperidinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-naphth-1-yl-1,4-hexahydro-1,4-diazepin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-carbamoyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-carbamoyl-3-2-(4-pyrimidin-2-yl-piperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-diethylcarbamoyl-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-Dihydro-5-methyl-6-diethylcarbamoyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-diethylcarbamoyl-3-2-(4-pyrimidin-2-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-quinazolin-4-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2,4-dimethoxyphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2,5-dimethylphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-naphth-1-yl-3,4-



dehydro-1-piperidinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR1D inhibitor according to the present invention is selected from those described in US6,159,979, including, without limitation, *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-4-bromonaphth-1-ylcarboxamide; 5-bromo-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylnaphth-1-ylcarboxamide; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylquinolin-4-ylcarboxamide; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-5-(pyridin-4-yl)naphth-1-ylcarboxamide; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-4-(pyridin-4-yl)naphth-1-ylcarboxamide; *N*-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-naphth-1-yl)urea; *N*-4-bromonaphth-1-yl-*N'*-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)urea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-4-(pyridin-4-yl)naphth-1-ylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-4-bromonaphth-1-ylacetamide; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-4-(pyridin-4-yl)naphth-1-ylacetamide; *N*-4-chloro-3-(4-methylpiperazin-1-yl)phenyl-*N'*-4-(pyridin-4-yl)naphth-1-ylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-naphth-1-ylthiourea; *N*-4-methoxy-3-(4-methylpiperidin-4-yl)phenyl-*N'*-4-(pyridin-4-yl)naphth-1-ylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-5,6,7,8-tetrahydronaphth-1-ylurea; *N*-benzo-2,1,3-thiadiazol-4-yl-*N'*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylurea; *N*-indol-4-yl-*N'*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-3,4-methylenedioxyphenylurea; *N*-5-bromonaphth-1-yl-*N'*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylurea; 5-bromo-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylnaphth-1-ylacetamide; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-2-methylquinolin-6-ylurea; *N*-isoquinolin-5-yl-*N'*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylurea; *N*-benzothiazol-6-yl-*N'*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N*-quinolin-3-ylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-quinolin-6-ylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-quinolin-5-ylurea; *N*-2,3-dihydrobenzofuran-5-yl-*N'*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylurea; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-4-(pyridin-3-yl)naphth-1-ylacetamide; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-5-(pyridin-3-yl)naphth-1-ylurea; 4-(4-Acetylphenyl)-*N*-4-methoxy-3-(4-

methylpiperazin-1-yl)phenylnaphth-1-ylacetamide; 4-(3-Acetylphenyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylnaphth-1-ylacetamide; 5-(3-Acetylphenyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylnaphth-1-ylacetamide; *N*-4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl-*N'*-5-phenylnaphth-1-ylurea; *N*-4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl-5-(pyridin-3-yl)naphth-1-ylacetamide; *N*-4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl-5-phenylnaphth-1-ylacetamide; 5-(4-Acetylphenyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylnaphth-1-ylacetamide; *N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-5-(2-methylphenyl)naphth-1-ylacetamide; *N*-4-bromo-3-(4-methylpiperazin-1-yl)phenyl-4-(pyridin-4-yl)naphth-1-ylacetamide; 5-(3,4-dimethoxyphenyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylnaphth-1-ylacetamide; *N*-5-(3-acetylphenyl)naphth-1-yl-*N'*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylurea; *N*-4-chloro-3-(1-methylpiperidin-4-yl)phenyl-4-(pyridin-4-yl)naphth-1-ylacetamide; 5-bromo-6-(4-methylpiperazin-1-yl)-1-5-(pyridin-4-yl)naphth-1-ylcarbonyl-1*H*-indole; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,166,034, including, without limitation, 5-4-{5-(5-methyl-1,3,4-oxadiazol-2-yl)-1-naphthyl}benzoyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-4-{5-(5-methyl-1,3,4-oxadiazol-2-yl)-1-naphthyl}benzoyl-2,3,5,6,7,8-methylspirofuro[2,3-*g*]quinoline-3,4'-piperidine; 5-4-{5-(5-methyl-1,3,4-oxadiazol-2-yl)-1-naphthyl}-3-methylbenzoyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-4-{5-(5-methyl-1,3,4-oxadiazol-2-yl)-1-naphthyl}-3-methylbenzoyl-2,3,5,6,7,8-hexahydro-1'-methylspirofuro[2,3-*g*]quinoline-3,4'-piperidine; 1'-methyl-5-4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-5-6-(2-methyl-4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)nicotinoyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,197,773, including, without limitation, 3,4-dichloro-*N*-(2-2-

(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 4-fluoro-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; *N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(1-methyl-2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(1-methyl-2-2-(4-methylpiperazin-1-yl)-phenyl-propyl)-benzamide; 3,4-dichloro-*N*-methyl-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; *N*-benzyl-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; *N*-(4-chlorobenzyl)-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(2-{2-methyl-(1-methylpyrrolidin-2-yl)methyl}-amino-phenyl)-ethyl)-benzamide; 3,4-dichloro-*N*-{2-2-(1-methyl-octahydro-pyrrolo[2,3-*c*]pyridin-6-yl)-phenyl-ethyl}-benzamide; 3,4-dichloro-*N*-{2-2-(hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-phenyl-ethyl}-benzamide; 3,4-dichloro-*N*-{2-2-(1-methylpiperidin-4-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-{2-2-(2-dimethylaminoethoxy)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-{2-2-(2-dimethylamino-ethylsulfanyl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-{2-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl-ethyl)-benzamide; 4-chloro-*N*-{2-2-(3-dimethylamino-pyrrolidin-1-yl)-phenyl-ethyl)-benzamide; 4-chloro-*N*-(2-{2-methyl-(2-morpholin-4-yl-ethyl)-amino-phenyl}-ethyl)-benzamide; 2-(4-chlorophenyl)-*N*-{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-acetamide; *N*-{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-*N*-phenylacetamide; *N*-{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-isonicotinamide; *N*-{2-2-(1-azabicyclo[2.2.2]oct-4-yl)-phenyl-ethyl}-*N*-methylbenzamide; *N*-{2-2-(1,4-dimethylpiperidin-4-yl)-phenyl-ethyl}-4-fluorobenzamide; 4-fluoro-*N*-{2-2-(9-methyl-3,9-diazabicyclo[3.3.1]non-3-yl)-phenyl-ethyl)-benzamide; *N*-(2-2-(1,4-diazabicyclo[3.3.1]non-4-yl)-phenyl-ethyl)-*N*-methylbenzamide; *N*-{1-methyl-2-2-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-phenyl-ethyl)-benzamide; 2,4-dichloro-*N*-methyl-*N*-{1-methyl-2-2-(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)-phenylethyl)-benzamide; *N*-{2-2-(4-methyloctahydroquinoxalin-1-yl)-phenyl-ethyl)-benzamide; *N*-{2-2-(1-ethylpyrrolidin-2-ylmethoxy)-phenyl-ethyl)-benzamide; 5-phenyloxazole-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-amide; 5-phenylthiophene-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-amide; 5-methylthiophene-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-amide; 4-fluoronaphthalene-1-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-amide; 5-fluoro-1*H*-indole-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-amide; 4-chloro-*N*-{2-2-

(3,4,5-trimethylpiperazin-1-yl)-phenyl-ethyl}-benzamide; 3,4-dichloro-*N*-{2-2-(2,4,5-trimethylpiperazin-1-yl)-phenyl-ethyl}-benzamide; 3,4-dichloro-*N*-{2-2-(2,4,6-trimethylpiperazin-1-yl)-phenyl-ethyl}-benzamide; and pharmaceutically acceptable salts or esters thereof.

- 5 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,342,498, including, without limitation, *N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)eth-1-yl)-3-(4-(6-fluoroindol-3-yl)-piperidin-1-yl)propenamide; *N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)eth-1-yl)-3-(4-(6-fluoroindol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl)propenamide; *N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)eth-1-yl)-3-(4-(6-chloroindol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl)propenamide; 1-(2-methoxyphenyl)-4-(6-(4-(6-chloroindole-3-yl)-1,2,3,6-tetrahydropyridin-1-yl)hex-1-yl)piperazine; *N*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)eth-1-yl)-3-(4-(6-chloroindol-3-yl)-piperidin-1-yl)propenamide; 1-(2-methoxyphenyl)-4-(6-(4-(6-fluoroindole-3-yl)-piperidin-1-yl)hex-1-yl)piperazine; 1-(2-methoxyphenyl)-4-(6-(4-(6-chloroindole-3-yl)-piperidin-1-yl)hex-1-yl)piperazine; and pharmaceutically acceptable salts or esters thereof.

- In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,346,622, including, without limitation, 3,3-dimethyl-2-3-(4-(5-tetralinyl)-1-piperazinyl)prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(2-phenyl-4-quinazolinyl)-1-piperazinyl)prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(2-quinolinyl)-1-piperazinyl)-prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-diazepanyl)-prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(4-chloro-1-phthalazinyl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-2-methyleneprop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(4-quinazolinyl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(1-naphthyl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-isoquinolin-4-yl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-prop-1-

yl-6-(1-pyrrolyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-prop-1-yl-6-benzoylamido-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-prop-1-yl-6-nitro-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(2,3-dimethylphenyl)-1-piperazinyl)eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(4-indanyl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(4-chloro-1-naphthyl)-1-piperazinyl)prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(2-pyrimidinyl)-1-piperazinyl)-prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(4-methoxyphenyl)-1-piperazinyl)eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(2-methoxyphenyl)-1-piperazinyl)-2-hydroxy-prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-diethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(2,5-dimethylphenyl)-1-piperazinyl)prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(2-cyanophenyl)-1-piperazinyl)eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(1-naphthyl)-1-piperazinyl)-eth-1-yl-4-chloro-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,355,647, including, without limitation, 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-acetyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-benzyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-(4-chlorophenyl-2-ethyl)-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-

carbethoxy-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-  
d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methyl-1-naphthyl)-1-  
piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-  
carbethoxy-3-2-(4-(2-methoxy-1-naphthyl)-1-  
5 piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-  
carbethoxy-3-2-(4-pyrimidin-2-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-  
d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methoxyphenyl)-1-  
piperidiny)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-  
(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-  
10 one; 3,4,5,7-tetrahydro-3-2-(4-naphth-1-yl)hexahydro-1,4-diazepin-1-  
yl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-(2-  
methylphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one;  
3,4,5,7-tetrahydro-3-2-(4-tetralin-5-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-  
d]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-indan-1-yl-1-  
15 piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-  
(4-(2-methoxyphenyl)-3,4-dehydro-1-piperidiny)ethylpyrrolo[3',4':4,5]thieno[2,3-  
d]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-naphth-1-yl-1-piperidiny)-  
ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-(2-  
methoxy-1-naphthyl-3,4-dehydro-1-piperidiny)ethylpyrrolo[3',4':4,5]thieno[2,3-  
20 d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(2-methoxyphenyl)-1-  
piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-  
ethyl-3-2-(4-(2,3-dimethylphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-  
d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(2-chlorophenyl)-1-  
piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-  
25 ethyl-3-2-(4-pyrimidin-2-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-  
d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-pyridin-2-yl-1-  
piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-  
ethyl-3-2-(4-quinolin-2-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-  
4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(2-methoxyphenyl)-1-  
30 piperidiny)ethylpyrrolo[3',4':4,5]thieno[2,3-d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-  
ethyl-3-3-(4-pyrimidin-2-yl-1-piperazinyl)propylpyrrolo[3',4':4,5]thieno[2,3-  
d]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-methyl-3-2-(4-(3-trifluoromethyl-phenyl)-1-

piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-methyl-3-2-(4-(2-cyano-phenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-methyl-3-2-(4-isoquinolin-4-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-methyl-3-2-(4-naphth-1-yl-3,4-dehydro-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-acetyl-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-acetyl-3-2-(4-(2-methyl-1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-benzyl-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-(4-nitrophenyl-2-ethyl)-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-(4-aminobenzyl)-3-2-(4-(2-methyl-1-naphthyl)-1-iperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methylphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-chlorophenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-phenyl-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-naphth-1-yl-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-naphth-1-yl-3,4-dehydro-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-3-(4-(2-cyanophenyl)-1-piperazinyl)propylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-indan-4-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,403,592, including, without limitation, 3-(4-chlorophenyl)-5-2-(4-methylpiperazin-1-yl)-benzylidene-imidazolidine-2,4-dione; 3-(4-chlorobenzyl)-5-2-(4-methylpiperazin-1-yl)-benzylidene-imidazolidine-2,4-dione; 3-(4-chlorobenzyl)-5-2-(4-methylpiperazin-1-yl)-benzylidene-thiazolidine-2,4-dione; 4-benzyl-2-2-(4-

methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorobenzyl)-2-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 3-(4-chlorophenyl)-5-2-(4-methylypiperazin-1-yl)-benzylidene-thiazolidine-2,4-dione; 3-(4-trifluoromethylphenyl)-5-2-(4-methylypiperazin-1-yl)-benzylidene-thiazolidine-2,4-dione; 2-2-(4-methylypiperazin-1-yl)-benzylidene-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-fluoro-6-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylypiperazin-1-yl)-benzylidene-morpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylypiperazin-1-yl)-benzyl-thiomorpholin-3-one; 4-methyl-2-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(2-piperazin-1-ylbenzylidene)-thiomorpholin-3-one; 4-benzyl-2-2-(4-methylypiperazin-1-yl)-benzylidene-1,1-dioxothiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-3-fluoro-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-5-fluoro-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylypiperazin-1-yl)-5-trifluoromethyl-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-4-(2-methoxyethyl)piperazin-1-yl-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-isopropylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-ethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3-chlorophenyl)-2-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 2-2-chloro-6-(4-methylypiperazin-1-yl)-benzylidene-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylypiperazin-1-yl)-4-trifluoromethyl-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylypiperazin-1-yl)-benzylidene-1-oxo-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(5-fluoro-2-piperazin-1-yl-benzylidene)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-3,6-difluoro-2-(4-methylypiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(3,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-phenyl-2-2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 2-5-fluoro-2-(4-methylypiperazin-1-yl)-benzylidene-4-phenyl-thiomorpholin-3-one; 4-benzol,3-dioxol-5-yl-2-2-(3,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 2-2-(4-tert-butylpiperazin-1-yl)-benzylidene-4-



(3,4-dichlorophenyl)-thiomorpholin-3-one; 3-(3,4-dichlorophenyl)-5-2-(4-methylpiperazin-1-yl)-benzylidene-thiazolidin-4-one; 3-4-(3,4-dichlorophenyl)-3-oxo-thiomorpholin-2-ylidenemethyl-6-dimethylamino-2-(4-methylpiperazin-1-yl)-benzonitrile; 5-2-(4-methylpiperazin-1-yl)-benzylidene-2-phenylthiazolidin-4-one; 4-  
 5 (3,4-dichlorophenyl)-2-2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-5-methyl-2-(4-methylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 2-4-chloro-2-(4-methylpiperazin-1-yl)-benzylidene-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-2-(3,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(2,4-difluorophenyl)-2-2-  
 10 (3,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 2-4-bromo-2-(4-methylpiperazin-1-yl)-benzylidene-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-2-(3,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-2-(3,4,5-trimethylpiperazin-1-yl)-  
 15 benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(octahydropyrido-[1,2- $\alpha$ ]pyrazin-2-yl)-benzylidene-thiomorpholin-3-one; 2-2-(4-cyclopropylpiperazin-1-yl)-benzylidene-4-pyridin-3-yl-thiomorpholin-3-one; 2-2-(4-cyclopropylpiperazin-1-yl)-benzylidene-4-(3,4-difluorophenyl)-thiomorpholin-3-one; 2-2-(4-cyclopropylpiperazin-1-yl)-benzylidene-4-(3,5-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-  
 20 2-2-(2,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-2-(2,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(3-methylaminopyrrolidin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-2-(2,4,5-trimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-benzo-1,3-dioxol-5-yl-2-2-(4-cyclopropylpiperazin-1-yl)-  
 25 benzylidene-thiomorpholin-3-one; 2-2-(3,5-dimethylpiperazin-1-yl)-benzylidene-4-(4-fluorophenyl)-thiomorpholin-3-one; 4-benzo-1,3-dioxol-5-yl-2-2-(2,5-dimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 2-2-(3,5-dimethylpiperazin-1-yl)-benzylidene-4-phenylthiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methyl-1,4-diazepan-1-yl)-benzylidene-  
 30 one;

thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(2,4,6-trimethylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 2-2-(4-cyclopropylpiperazin-1-yl)-benzylidene-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 5-2-(4-methylpiperazin-1-yl)-benzylidene-thiazolidine-2,4-dione; 2-2,4-dibromo-6-(4-methylpiperazin-1-yl)-benzylidene-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-1,4-oxazepan-3-one; 4-(4-chlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-1,4,5-oxadiazepan-3-one; 4-(4-chlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-1,4-thiazepan-3-one; 4-(3,4-dichlorophenyl)-2-{2-(2-dimethylaminoethyl)-methyl-amino-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(1-methylpiperidin-4-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(1,4-dimethylpiperidin-4-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-thiomorpholine-3,5-dione; 4-(3,4-dichlorophenyl)-2-2-(2-dimethylaminoethoxy)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(4-isopropylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(1-methylpyrrolidin-3-ylmethyl)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-methyl-(1-methylpyrrolidin-2-ylmethyl)-amino-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-2-(1-methylpyrrolidin-2-yl)-ethyl-benzylidene}-thiomorpholin-3-one; 1-(3,4-dichlorophenyl)-4-methyl-3-2-(4-methylpiperazin-1-yl)-benzylidene-piperazin-2-one; 4-methyl-3-2-(4-methylpiperazin-1-yl)-benzylidene-1-(4-trifluoromethylphenyl)-piperazin-2-one; 1-(4-chlorophenyl)-4-methyl-3-2-(4-methylpiperazin-1-yl)-benzylidene-piperazin-2-one; 2-2-(4-methylpiperazin-1-yl)-benzylidene-4-(4-trifluoromethylphenyl)-morpholin-3-one; 2-4-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-{1-2-(4-methylpiperazin-1-yl)-phenyl-ethylidene}-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-2-(4-methylpiperazin-1-yl)-benzyl-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 4-(4-chlorophenyl)-6-methyl-2-2-(4-methylpiperazin-1-yl)-benzylidene-thiomorpholin-3-one; 3-(4-chlorophenyl)-2,2-dimethyl-5-2-(4-methylpiperazin-1-yl)-benzylidene-thiazolidin-4-one; 4-(4-chlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-1,4-oxazepan-3-one; 4-(4-

chlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-4*H*-1,4-thiazin-3-one; 1-(4-chlorophenyl)-4,6,6-trimethyl-3-2-(4-methylpiperazin-1-yl)-benzylidene-piperazin-2-one; 1-(4-chlorophenyl)-4-methyl-3-2-(4-methylpiperazin-1-yl)-benzylidene-piperazin-2-one; 4-(4-chlorophenyl)-2-2-(4-methylpiperazin-1-yl)-benzylidene-morpholin-3-one; 5 3-(4-chlorophenyl)-5-2-(4-methylpiperazin-1-yl)-benzylidene-oxazolidin-4-one; 3-(4-chlorophenyl)-2,2-dimethyl-5-2-(4-methylpiperazin-1-yl)-benzylidene-imidazolidin-4-one; 3-(4-chlorophenyl)-5-2-(4-methylpiperazin-1-yl)-benzylidene-imidazolidin-4-one; and pharmaceutically acceptable salts thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,509,340, including, without limitation, *N*-2-(5-fluoro-3-indolyl)ethyl-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenylurea; 4-(5-cyano-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(6-fluoro-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 3-{1-4-methoxy-3-(4-methyl-1-piperazinyl)phenylaminocarbonyl-4-piperidyl}indole-5-carboxamide; 4-(5-fluoro-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-2-(3-indolyl)ethyl-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(4-fluoro-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(7-methoxyindol-3-yl)piperidine-1-carboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-amide; 4-4-(5-fluoro-3-indolyl)butylpiperazine-1-carboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenylamide; 4-(5-cyanoindol-3-yl)-3,6-dihydro-2*H*-pyridine[*lacuna*]1-carboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenylamide; 3-(5-fluoroindol-3-yl)pyrrolidine-1-carboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-amide; 4-(5-fluoroindol-3-yl)cyclohexanecarboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenylamide; *N*-2-(5-hydroxy-3-indolyl)ethyl-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenylurea; *N*-{2-4-(6-fluoro-3-indolyl)piperidin-1-ylethyl}-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-urea; *N*-4-(5-cyano-3-indolyl)butyl-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenylurea; 4-4-(5-cyano-3-indolyl)butylpiperazine-1-carboxylic acid 4-methoxy-3-(4-methyl-1-piperazinyl)-phenylamide; 4-(5-fluoroindol-3-yl)piperidine-1-carboxylic acid (2,3-dihydro-1'-

methylspiro(benzofuran)-3,4-piperidin)amide; *N*-{2-4-(6-fluoro-3-indolyl)piperidin-1-ylethyl}-2,3-dihydro-1-methylspiro(benzofuran)-3,4-piperidinurea; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,537,995, including, without limitation, 5-2-(4-methylpiperazin-1-yl)-phenyl-furan-2-carboxylic acid 4-chlorobenzylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-furan-2-carboxylic acid 4-chlorophenylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-thiophene-2-carboxylic acid 4-chlorophenylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-furan-2-carboxylic acid 2-(4-chlorophenyl)ethyl-amide; 4-2-(4-methylpiperazin-1-yl)-phenyl-furan-2-carboxylic acid 4-chlorobenzylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-thiophene-2-carboxylic acid benzylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-thiophene-2-carboxylic acid 4-fluorobenzylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-thiophene-2-carboxylic acid 4-methoxybenzylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-thiophene-2-carboxylic acid 2-(4-chlorophenyl)ethyl-amide; 3-methyl-5-2-(4-methylpiperazin-1-yl)-phenyl-thiophene-2-carboxylic acid 4-chlorobenzylamide; 5-5-fluoro-2-(4-methylpiperazin-1-yl)-phenyl-thiophene-2-carboxylic acid 4-chlorobenzylamide; 5-2-(4-methylpiperazin-1-yl)-phenyl-1H-pyrrole-2-carboxylic acid 4-chlorobenzylamide; and pharmaceutically acceptable salts thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US6,887,905, including, without limitation, (7*R*,9*aS*)-*trans*-1-{3-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-benzyl}-azetidin-3-ol; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-morpholin-4-ylmethylphenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-1-(3-{1-[2-(benzo[*d*]isoxazol-3-yl-methyl-amino)-ethyl]-6-methyl-piperidin-3-ylmethoxy}-benzyl)-azetidin-3-ol; (7*R*,9*aS*)-*trans*-2-(4-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-1-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]pyrrolidine-3,4-diol; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-

octahydropyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(2-methyl-5-pyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(3-methoxy-5-pyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(4-chloro-3-pyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(4-pyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-7-(3-azetidin-1-ylmethyl-phenoxy-methyl)-2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-cyclopropylmethyl-amine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[3-(2-methoxymethyl-pyrrolidin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-cyclopropyl-amine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(3-pyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[3-(4-ethyl-piperazin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-cyclohexyl-amine; (7*S*,9*aS*)-*cis*-1-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyridol[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-pyrrolidin-3-ol; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[3-(2,5-dimethyl-[pyrrolidin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[3-(2,5-dimethyl-pyrrolidin-1-ylmethyl)-phenoxy-methyl]-octahydro-pyridol[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-1-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-pyrrolidine-3,4-diol; (7*S*,9*aS*)-*cis*-1-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-pyrrolidin-3-ol; (7*S*,9*aS*)-*cis*-[3-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-benzyl]-isobutyl-amine; (7*S*,9*aS*)-*cis*-benzo[*d*]isoxazol-3-yl-methyl-{2-[2-methyl-5-(2-morpholin-4-ylmethyl-phenoxy-methyl)-piperidin-1-yl]-ethyl}-amine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(2-pyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyridol[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(4-morpholin-4-ylmethyl-phenoxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(4-pyrrolidin-1-ylmethyl-phenoxy-methyl)-octahydro-pyridol[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(7-fluoro-benzo[*d*]isoxazol-3-yl)-7-

- (3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(6-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(6,7-difluoro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine;
- 5 (7*R*,9*aS*)-*trans*-3-{3-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-benzyl}-3-aza-bicyclo[3.2.2]nonane; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-*cis*-octahydro-isoindol-2-ylmethyl)-phenoxyethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(2-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-
- 10 pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-chloro-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-methyl-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl)-7-(2-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*cis*-
- 15 2-benzo[*d*]isoxazol-3-yl)-7-(2-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(2-morpholin-4-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(4-morpholin-4-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(2-methoxy-benzo[*d*]isoxazol-3-yl)-
- 20 7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-(5-methoxy-benzo[*d*]isoxazol-3-yl)-7-(3-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(3-(2-methoxymethyl-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-(2-methoxymethyl-pyrrolidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-(2-methoxymethyl-piperidin-1-ylmethyl-phenoxyethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[3-(3-methoxymethyl-piperidin-1-ylmethyl)-phenoxyethyl]-octahydro-pyrido[1,2-*a*]; and pharmaceutically acceptable salts or esters thereof.
- 30 In one embodiment, the 5-HTR1D inhibitor according to the present invention is selected from those described in US6,924,289, including, without limitation, 3-[2-(4-

methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 6-chloro-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one;  
 methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 5-chloro-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one;  
 methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 1-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-phenyl-1,3-dihydro-indol-2-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-dichlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,3-dihydro-indol-2-one; 1-(4-chlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(4-chlorobenzyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-difluorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(2,4-dichlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(4-chlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(3,4-dichlorobenzyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(4-chlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(3,4-dichlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-phenyl-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-(4-trifluoromethylphenyl)-pyrrolidin-2-one; 1-(3,4-difluorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(4-methoxyphenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-3,4-dihydro-1*H*-quinolin-2-one; 1-(3,4-dichlorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-phenyl-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-(*p*-tolyl)-pyrrolidin-2-one; 3-[4-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-1-phenyl-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-fluoro-6-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 1-(3,4-difluorophenyl)-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidine-2-one; 1-[2-(4-chlorophenyl)ethyl]-3-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-piperidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(2-dimethylaminoethoxy)-benzylidene]-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-(4-

trifluoromethylphenyl)-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-azetidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-azepin-2-one; 1-(3,4-dichlorophenyl)-3-{1-[2-(4-methylpiperazin-1-yl)phenyl]ethyl}-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-{1-[2-(4-methylpiperazin-1-yl)phenyl]ethyl}-piperidine-2-one; 1-(3,4-dichlorophenyl)-3-{1-[2-(4-methylpiperazin-1-yl)phenyl]-ethylidene}-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-{1-[2-(4-methylpiperazin-1-yl)phenyl]-ethylidene}-piperidin-2-one; 1-(3,4-dichlorophenyl)-3-{[2-(4-methylpiperazin-1-yl)phenyl]-phenylmethylene}-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-{2-[(2-dimethylaminoethyl)-methylamino]-benzylidene}-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(pyrrolidin-1-ylethoxy)-benzylidene]-pyrrolidin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(2-dimethylaminoethylamino)-benzylidene]-pyrrolidin-2-one; 2-(3,4-dichlorophenyl)-3-[2-(2-dimethylaminoethylamino)-benzylidene]-pyrrolidin-2-one; 2-(3,4-dichlorophenyl)-4-[2-(4-methylpiperazin-1-yl)-benzylidene]-octahydro-isoquinolin-3-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-octahydro-quinolin-2-one; 1-(3,4-dichlorophenyl)-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-octahydro-indol-2-one; 1-(3,4-dichlorophenyl)-5,5-dimethyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-pyrrolidin-2-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US7,026,314, including, without limitation, 8-(4-methyl-1-piperazinyl)-*N*-[4-(4-morpholinyl)phenyl]-4-oxo-4*H*-chromene-2-carboxamide; 2-{1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one, 2-{1-[4-(1-acetyl-2,3-dihydro-1*H*-indol-6-yl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 2-chloro-5-(4-{1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-piperazin-1-yl)-benzonitrile; 2-{1-[4-(4-methoxyphenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-furan-2-yl-1*H*-pyrazol-3-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-imidazol-1-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-[1,2,3]thiadiazol-5-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid 4-



[1,2,3]thiadiazol-5-yl-benzylamide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2,5-diethoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-cyanomethyl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (1*H*-indol-5-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(2,6-dimethyl-morpholin-4-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-fluoro-phenoxy)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-2-(6-morpholin-4-yl-benzooxazol-2-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-hydroxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-ethoxy-benzothiazol-2-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-bromo-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 4-[4-({1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-

piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(2,6-dimethyl-morpholin-4-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-dimethylsulfamoyl-piperazin-1-yl)-phenyl]-amide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid dimethylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid ethylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid cyclohexylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid cyclopentylamide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(1-pyrrolidin-1-yl-methanoyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(propane-2-sulfonyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-methyl-propanoyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-

carboxylic acid {4-[4-(1-morpholin-4-yl-methanoyl)-piperazin-1-yl]-phenyl}-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-  
 5 fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 10 carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-  
 15 amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-chloro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 20 carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-amide; 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-  
 25 piperazin-1-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-  
 30 amide; *N*-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-4-morpholin-4-yl-benzamide; 8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid(4-morpholin-4-yl-phenyl)-amide; (+)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-

morpholin-4-yl-phenyl)-amide; (-)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; racemic-8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (faster running isomer); 8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (slower running isomer); 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid ethylamide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-4-oxo-8-piperazin-1-yl-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-hydroxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid(4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 8-[(2-dimethylamino-ethyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[(3-dimethylamino-propyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*R*)-(+)-3-dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*S*)-(-)-3-dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-[methyl-(1-methyl-pyrrolidin-3-yl)-amino]-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[ethyl-(1-ethyl-pyrrolidin-3-yl)-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 4-dimethylamino-6-methoxy-8-(4-methyl-piperazin-1-

yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-4-methylamino-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-oxo-8-piperazin-1-yl-4H-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US7,425,574, including, without limitation, 4-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid methyl ester; 5-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid ethyl ester; 6-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid ethyl ester; 4-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid amide; 7-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid ethyl ester; 7-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid methyl ester; 7-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid amide; 7-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid; 5-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid amide; 5-{2-[2-(5-fluoro-1H-indol-3-yl)ethylamino]ethoxy}benzofuran-2-carboxylic acid amide; 6-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid amide; 5-bromo-7-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid methyl ester; 5-bromo-7-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}benzofuran-2-carboxylic acid amide; 7-{2-[2-(5-fluoro-1H-indol-3-yl)ethylamino]ethoxy}benzofuran-2-carboxylic acid amide; 7-{2-[4-(5-cyano-1H-indol-3-yl)butylamino]ethoxy}-5-nitrobenzofuran-2-carboxylic acid amide; 7-{2-[2-(5-cyano-1H-indol-3-yl)ethylamino]ethoxy}benzofuran-2-carboxylic acid amide; 7-{3-[2-(5-cyano-1H-indol-3-yl)ethylamino]propoxy}benzofuran-2-carboxylic acid amide; 7-{3-[2-(5-fluoro-1H-indol-3-yl)ethylamino]propoxy}benzofuran-2-carboxylic acid amide; and pharmaceutically acceptable salts or esters thereof.

- In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US7,432,282, including, without limitation, 3-{4-[(5-bromopyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(pyridin-2-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(pyridin-4-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-(4-{[5-(4-fluorophenyl)pyridin-3-ylmethyl]amino}butyl)-1*H*-indole-5-carbonitrile; 3-{4-[(quinolin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-[4-(2-pyridin-4-ylethylamino)butyl]-1*H*-indole-5-carbonitrile; 3-{4-[(2,6-dichloropyridin-4-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(2-chloro-6-methylpyridin-4-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(2-chloropyridin-4-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(2-methylpyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(6-chloropyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-(4-{[2-(4-chlorophenoxy)pyridin-3-ylmethyl]amino}butyl)-1*H*-indole-5-carbonitrile; 3-{4-[(2-methylsulfanylpyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(2,5-dichloropyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(2,6-dichloropyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(5-methylpyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(6-trifluoromethylpyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(quinolin-2-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(4-phenylpyridin-2-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(quinolin-4-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(4-phenylpyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(5-cyano-6-methylsulfanylpyridin-2-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(5-phenylpyridin-3-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-{4-[(5-phenylpyridin-2-ylmethyl)amino]butyl}-1*H*-indole-5-carbonitrile; 3-[4-(methylpyridin-3-ylmethylamino)butyl]-1*H*-indole-5-carbonitrile; and pharmaceutically acceptable salts or esters thereof.
- In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US7,776,860, including, without limitation, 3-amino-8-(1-

piperazinyl)-2*H*-1-benzopyran-2-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US9,938,277, including, without limitation, 3-((6*aR*,9*S*,10*aR*)-5-cyclopropyl-7-methyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinolin-9-yl)-1,1-diethylurea; (6*aR*,9*R*)-5-cyclopropyl-*N*-((*S*)-1-hydroxybutan-2-yl)-4,7-dimethyl-4,6,6*a*,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (6*aR*,9*R*)-5-cyclopropyl-*N*-((*S*)-1-hydroxybutan-2-yl)-4,7-dimethyl-4,6,6*a*,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (6*aR*,9*R*,10*aS*)-*N*-((*S*)-1-hydroxybutan-2-yl)-10*a*-methoxy-4,7-dimethyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (6*aR*,9*R*,10*aS*)-*N*-((*S*)-1-hydroxybutan-2-yl)-10*a*-methoxy-4,7-dimethyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (6*aR*,9*R*,10*aS*)-*N*-((*S*)-1-hydroxybutan-2-yl)-10*a*-methoxy-4,7-dimethyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US20030064995, including, without limitation, *N*-[2-(5-fluoro-3-indolyl)ethyl]-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; 4-(5-cyano-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(6-fluoro-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 3-{1-[4-methoxy-3-(4-methyl-1-piperazinyl)phenylaminocarbonyl]-4-piperidyl}indole-5-carboxamide; 4-(5-fluoro-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-[2-(3-indolyl)ethyl]-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(4-fluoro-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(7-methoxyindol-3-yl)piperidine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; 4-[4-(5-fluoro-3-indolyl)butyl]piperazine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; 4-(5-cyanoindol-3-yl)-3,6-dihydro-2*H*-pyridine[*lacuna*]1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-

yl)phenyl]amide; 3-(5-fluoroindol-3-yl)pyrrolidine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; 4-(5-fluoroindol-3-yl)-cyclohexanecarboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; *N*-[2-(5-hydroxy-3-indolyl)ethyl]-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; *N*-{2-[4-(6-fluoro-3-indolyl)piperidin-1-yl]ethyl}-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; *N*-[4-(5-cyano-3-indolyl)butyl]-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; 4-[4-(5-cyano-3-indolyl)butyl]piperazine-1-carboxylic acid [4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]amide; 4-(5-fluoroindol-3-yl)piperidine-1-carboxylic acid (2,3-dihydro-1'-methylspiro(benzofuran)-3,4-piperidin) amide; *N*-{2-[4-(6-fluoro-3-indolyl)piperidin-1-yl]ethyl}-[2,3-dihydro-1-methylspiro(benzofuran)-3,4-piperidin]urea; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US20030212109, including, without limitation, 3,3-dimethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-methyl-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-methylthio-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-methylthio-3-phenylmethyl-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-phenylmethyl-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-methyl-3-phenylmethyl-1,3-dihydro-2*H*-indol-2-one; 3-Ethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-methyl-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-(1-methylethyl)-3-methylthio-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-(1-methylethyl)-1,3-dihydro-2*H*-indol-2-one; 5-bromo-3,3-dimethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2*H*-indol-2-one; 3,3-dimethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-5-methanesulfonyl-1,3-dihydro-2*H*-indol-2-one; 3,3-dimethyl-5-fluoro-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2*H*-indol-2-one; 5,6-difluoro-3,3-dimethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2*H*-indol-2-one; 3,3-dimethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-4-methoxy-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,5-trimethyl-1,3-dihydro-2*H*-indol-2-one;



5-chloro-3,3-dimethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,7-trimethyl-1,3-dihydro-2*H*-indol-2-one; 3,3-dimethyl-1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-5-methoxy-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,4-trimethyl-indol-2(3*H*)-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,6-trimethyl-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-5-fluoro-1,3-dihydro-2*H*-indol-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3-difluoro-1,3-dihydro-2*H*-indole-2-one; 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,5-trifluoro-1,3-dihydro-2*H*-indole-2-one; 1-(2-(4-(4-fluorobenzoyl)-1-piperidinyl)-1-ethyl)-1,3-dihydro-3-spiro-1-cyclopropyl-2*H*-indole-2-one; 1-(2-(4-(4-fluorobenzoyl)-1-piperidinyl)-1-ethyl)-3-methyl-3-phenyl-1,3-dihydro-2*H*-indol-2-one; 1-(2-(4-(4-fluorobenzoyl)-1-piperidinyl)-1-ethyl)-1*H*-indol-2,3-dione monohydrochloride; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US20050085457, including, without limitation, 8-(4-methyl-1-piperazinyl)-*N*-[4-(4-morpholinyl)phenyl]-4-oxo-4*H*-chromene-2-carboxamide; 2-{1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 2-{1-[4-(1-acetyl-2,3-dihydro-1*H*-indol-6-yl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 2-chloro-5-(4-{1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl)-piperazin-1-yl)-benzonitrile; 2-{1-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-furan-2-yl-1*H*-pyrazol-3-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-imidazol-1-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-[1,2,3]thiadiazol-5-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid 4-[1,2,3]thiadiazol-5-yl-benzylamide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-

amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2,5-diethoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-cyanomethyl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (1*H*-indol-5-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(2,6-dimethyl-morpholin-4-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-fluoro-phenoxy)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-2-(6-morpholin-4-yl-benzooxazol-2-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-hydroxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-ethoxy-benzothiazol-2-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-bromo-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 4-[4-({1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-

piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-  
 amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid  
 [4-(2,6-dimethyl- morpholin-4-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-  
 yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 6-  
 5 methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-  
 hydroxy-ethyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-  
 4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide;  
 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-  
 cyano-4-morpholin-4-yl-phenyl)-amide; 4-[4-({ 1-[6-methoxy-8-(4-methyl-piperazin-1-  
 10 yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid  
 tert-butyl ester; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-  
 yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-  
 amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid  
 15 [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-  
 1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-dimethylsulfamoyl-piperazin-1-yl)-  
 phenyl]-amide; 4-[4-({ 1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-  
 yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid dimethylamide; 4-[4-({ 1-  
 [6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-  
 20 phenyl]-piperazine-1-carboxylic acid ethylamide; 4-[4-({ 1-[6-methoxy-8-(4-methyl-  
 piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-  
 carboxylic acid cyclohexylamide; 4-[4-({ 1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-  
 oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid  
 cyclopentylamide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 25 carboxylic acid {4-[4-(1-pyrrolidin-1-yl- methanoyl)-piperazin-1-yl]- phenyl}-amide; 6-  
 methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-(4-  
 (propane-2-sulfonyl)-piperazin-1-yl)-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-  
 1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-methyl-propanoyl)-piperazin-1-  
 yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 30 carboxylic acid {4-(4-(1-morpholin-4-yl-methanoyl)-piperazin-1-yl)-phenyl}-amide; 6-  
 fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-  
 morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-

chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-chloro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-amide; 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-ethane sulfonyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-amide; *N*-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-4-morpholin-4-yl-benzamide; 8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; (+)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; (-)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; racemic-8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-

yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (faster running isomer); 8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (slower running isomer); 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid  
 5 ethylamide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-4-oxo-8-piperazin-1-yl-4*H*-chromene-2-  
 10 carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-hydroxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-  
 15 8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 8-[(2-dimethylamino-ethyl)-methyl-amino]-6-  
 20 methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[(3-dimethylamino-propyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*R*)-(+)-3-dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*S*)-(-)-3-dimethylamino-pyrrolidin-1-yl)-6-  
 25 methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-[methyl-(1-methyl-pyrrolidin-3-yl)-amino]-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[ethyl-(1-ethyl-pyrrolidin-3-yl)-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 4-dimethylamino-6-methoxy-8-(4-methyl-piperazin-1-  
 30 yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-4-methylamino-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-

carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-oxo-8-piperazin-1-yl-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US20060009448, including, without limitation, 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-piperazin-1-yl)-benzylidene]-thiomorpholin-3-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in US20070010526, including, without limitation, 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-piperidin-1-ylmethyl-phenyl)-ethanone; 2-(4-isopropyl-phenyl)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methoxy-8-phenyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 1-[5-benzyloxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-isopropyl-phenyl)-ethanone; 1-[5-hydroxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-isopropyl-phenyl)-ethanone; 2-(4-isopropyl-phenyl)-1-(5-methoxy-8-pyridin-4-yl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanone; 2-(4-isopropyl-phenyl)-1-[5-methoxy-8-(1-methyl-1,2,3,6-tetrahydro-pyridinyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-6-propyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-propyl-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-propyl-benzenesulfonamide; *N*-isopropyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-tert-butyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-benzyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-(2-methoxybenzyl)-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-(3-methoxybenzyl)-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-

benzenesulfonamide; *N*-(4-methoxy-benzyl)-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*H*-(2-methoxy-phenyl)-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*H*-(3-methoxy-phenyl)-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*H*-(4-methoxy-phenyl)-benzenesulfonamide; *N*-cyclopropyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-cyclobutyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-methyl-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-ethyl-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N,N*-dimethyl-benzenesulfonamide; *N*-ethyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-methyl-benzenesulfonamide; *N,N*-diethyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N,N*-dipropyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-benzyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-methyl-benzenesulfonamide; *N*-benzyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-ethyl-benzenesulfonamide; *N*-benzyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-isopropyl-benzenesulfonamide; 2-[4-(azetidine-1-sulfonyl)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-ethanone; *N*-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-isonicotinamide; *N*-{4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-isonicotinamide; *N*-{5-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-

isonicotinamide; quinoline-5-carboxylic acid {2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-amide; quinoline-5-carboxylic acid {4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-amide; quinoline-5-carboxylic acid {5-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-amide; *N*-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzamide; *N*-{3-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-3-oxo-propyl}-benzamide; *N*-{4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-benzamide; *N*-{5-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-benzamide; 4-methoxy-*N*-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzamide; 4-methoxy-*N*-{4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-benzamide; 4-methoxy-*N*-{5-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-benzamide; (4-butylamino-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4-cyclohexyl-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4-benzyl-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4'-ethyl-biphenyl-4-yl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4'-hydroxy-biphenyl-4-yl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; [5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-(4-phenoxy-phenyl)-methanone; (4-benzoyl-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4-methoxy-phenylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-phenylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-methoxy-phenylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(3-methoxy-phenylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-benzylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-methoxy-benzylsulfamoyl)-phenyl]-amide; 5-



methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(3-methoxy-benzylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4-methoxy-benzylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-propylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-isopropylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-cyclopropylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-tert-butylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-methylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-ethylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-cyclobutylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(thiazol-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-acetylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-butyrylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(methyl-phenyl-sulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(acetyl-methyl-sulfamoyl)-phenyl]-amide; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-morpholin-4-yl-phenyl)-ethanone; 2-(4-bromo-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-dimethylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(3-morpholin-4-yl-phenyl)-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-piperidin-1-yl-phenyl)-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-[4-(4-propyl-piperidin-1-yl)-phenyl]-ethanone; 2-{4-[4-(2-methoxy-ethyl)-piperidin-1-yl]-phenyl}-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-

1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-  
 1*H*-isoquinolin-2-yl]-2-[4-(4-methyl-piperidin-1-yl)-phenyl]-ethanone; 2-[4-(4-  
 hydroxy-piperidin-1-yl)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-  
 5 phenyl}-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
 ethanone; 2-(4-amino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-  
 1*H*-isoquinolin-2-yl]-ethanone; 2-(4-isopropyl-phenoxy)-1-[5-methoxy-8-(4-methyl-  
 piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-[4-(4-benzyl-piperazin-1-  
 yl)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-  
 10 yl]-ethanone; 2-(4-isopropyl-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinolin-2-yl]-ethanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinoline-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 4-  
 amino-*N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-  
 yl]-2-oxo-ethyl}-phenyl)-butyramide; 2-(4-dibutylamino-phenyl)-1-[5-methoxy-8-(4-  
 15 methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-butylamino-  
 phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
 ethanone; 2-(4-diphenethylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-  
 3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-  
 3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-phenethylamino-phenyl)-ethanone; 2-{4-[Bis-(2-  
 20 benzyloxy-ethyl)-amino]-phenyl}-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-[4-(2-benzyloxy-ethylamino)-phenyl]-1-[5-  
 methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone;  
 biphenyl-4-yl-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-  
 yl]-methanone; 2-biphenyl-4-yl-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-  
 25 1*H*-isoquinolin-2-yl]-ethanone; 1-(5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-  
 1*H*-isoquinolin-2-yl)-2-(4-methoxy-phenyl)-ethanone; 2-benzo[1,3]dioxol-5-yl-1-[5-  
 methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-  
 (3,4-dimethoxy-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-  
 isoquinolin-2-yl]-ethanone; 2-(4-fluoro-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-  
 30 yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-chloro-phenyl)-1-[5-methoxy-8-(4-  
 methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-methyl-  
 phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-

ethanone; 2-phenyl-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-methylsulfanyl-phenyl)-ethanone; 2-(4-methanesulfinyl-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone;  
5 *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-methanesulfonamide; 2-[4-(2-methoxy-benzylamino)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-benzylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-[4-(3-methoxy-benzylamino)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone;  
10 2-[4-(4-methoxy-benzylamino)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-isopropyl-phenyl)-1-[5-methoxy-8-(4-methyl-piperazine-1-carbonyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3',4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-isopropyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-cyclohexyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(5-methoxy-pyrimidin-2-ylsulfamoyl)-phenyl]-amide; (4-{[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]-amino)-benzyl)-phosphonic acid diethyl ester; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(3,4-dimethyl-isoxazol-5-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(6-methyl-benzothiazol-2-yl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-tert-butyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-sulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-phenyl-2*H*-pyrazol-3-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(pyrrolidine-1-sulfonyl)-phenyl]-amide;  
25 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4,5-dimethyl-oxazol-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-

1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-phenyl-2*H*-pyrazol-3-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4-methyl-pyrimidin-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid

5 [4-(2,6-dimethyl-pyrimidin-4-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(pyrimidin-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2,6-dimethoxy-pyrimidin-4-ylsulfamoyl)-phenyl]-amide;

10 carboxylic acid [4-(6-methoxy-pyridazin-3-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4,6-dimethyl-pyrimidin-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(6-methoxy-pyrimidin-4-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-

15 isoquinoline-2-carboxylic acid [4-(pyridin-2-ylsulfamoyl)-phenyl]-amide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzoic acid methyl ester; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-methyl-benzamide; 8-(4-ethyl-piperazin-1-yl)-5-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-propylsulfamoyl-phenyl)-

20 amide; 8-(4-cyclohexyl-piperazin-1-yl)-5-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-propylsulfamoyl-phenyl)-amide; 2-(4-isopropyl-phenyl)-1-(5-methoxy-8-piperazin-1-yl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanone; *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-2-phenyl-acetamide; *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-

25 dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-3-phenyl-propionamide; *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-benzamide; *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-benzenesulfonamide; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-

30 phenylmethanesulfonyl-methyl-phenyl)-ethanone; 4-chloro-*N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-benzenesulfonamide; 4-tert-butyl-*N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-

dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-benzenesulfonamide; *N*-benzyl-*N*-  
 (4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-  
 ethyl}-phenyl)-benzenesulfonamide; 1-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-  
 3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-3-(4-methoxy-phenyl)-urea; 1-  
 5 (4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-  
 ethyl}-phenyl)-3-(3-methoxy-phenyl)-urea; [5-methoxy-8-(4-methyl-piperazin-1-yl)-  
 3,4-dihydro-1*H*-isoquinolin-2-yl]-[2'-methyl-4'-(5-methyl-[1,2,4]oxadiazol-3-yl)-  
 biphenyl-4-yl]-methanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-  
 isoquinoline-2-carboxylic acid (4-piperidin-1-yl-phenyl)-amide; 5-methoxy-8-(4-  
 10 methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4-methyl-  
 piperazin-1-yl)-phenyl]-amide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected  
 from those described in WO1994015920, including, without limitation, *N*-[4-methoxy-3-  
 (4-methyl-1-piperazinyl)phenyl]-2-methyl-4'-(1-methyl-1*H*-pyrazol-3-yl)[1,1'-  
 15 biphenyl]-4-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-  
 4'-(2-methyl-4-thiazolyl)[1,1'-biphenyl]-4-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-  
 piperazinyl)phenyl]-2'-methyl-4'-(2-oxazolyl)[1,1'-biphenyl]-4-carboxamide; *N*-[4-  
 methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-2-oxazolyl)[1,1'-  
 biphenyl]-4-carboxamide; *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-  
 20 4'-(1,3-oxathiolan-2-yl)[1,1'-biphenyl]-4-carboxamide; 4'-(4,5-dihydro-2-oxazolyl)-*N*-  
 [4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl[1,1'-biphenyl]-4-  
 carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected  
 from those described in WO1995011243, including, without limitation, 4-bromo-3-  
 25 methyl-*N*-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide; 4-  
 bromo-3-methyl-*N*-[7-(piperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide; 4-  
 bromo-3-methyl-*N*-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide; 4-(4-  
 pyridyl)-3-methyl-*N*-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-  
 yl]benzamide; 4-(4-pyridyl)-3-methyl-*N*-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-  
 30 7-yl]benzamide; *N*-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-

2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[7-(piperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; 4-bromo-3-methyl-*N*-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]benzamide; *N*-[7-(piperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; 4-bromo-3-methyl-*N*-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]benzamide; *N*-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[7-(piperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HT<sub>1D</sub> inhibitor according to the present invention is selected from those described in WO1995030675, including, without limitation, *N*-[3-((*S*)-1-methylpyrrolidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-((*R*)-1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-((*R*)-pyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-(1-methylazetidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[3-(azetidin-2-ylmethoxy)-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-(1-methylpiperidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-(1-methylazepin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-(1-methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-(1-methylpiperidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-(1-methylpyrrolidin-3-yloxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-methoxy-3-(3-quinuclidinyloxy)phenyl]-2'-methyl-4'

- (5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; 4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-chloro-3-(1-methylpyrrolidin-2-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; *N*-[4-(1-methylpiperidin-3-ylmethoxy)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide; 5-chloro-2,3-dihydro-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(1-methylpyrrolidin-2-ylmethoxy)-1*H*-indole; 2,3-dihydro-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-[2-(1-methylpyrrolidin-2-yl)ethyl]-1*H*-indole; and pharmaceutically acceptable salts or esters thereof.
- 10 In one embodiment, the 5-HTR1D inhibitor according to the present invention is selected from those described in WO1999029666, including, without limitation, 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline; 5-chloro-6-(4-ethylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline; 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-chloro-1-(9-oxo-9H-fluoren-2-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline; 5-chloro-1-(9-oxo-9H-fluoren-3-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline; 5-methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline; 5-methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from those described in WO1999031086, including, without limitation, *N*-[3-chloro-4-(pyridin-4-yl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[4-(pyridin-4-yl)naphth-1-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-(pyridin-4-yl)naphth-1-yl]-urea; 4-bromo-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide; 5-bromo-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-4-(pyridin-4-yl)naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-5-(pyridin-4-yl)naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]-urea; *N*-[3-cyano-4-(pyridin-4-yl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-5-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-8-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-3-yl]-urea; 2,2-dichloro-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; 5-(4-acetylphenyl)-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-4-yl]-urea; *N*-[3-chloro-4-(pyridin-4-yl)phenyl]-*N'*-[4-(1-methylpiperidin-4-yl)quinolin-6-yl]-urea; *N*-[3-methyl-4-(6-methylpyridin-2-yl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(2,6-dimethylpyridin-4-yl)-3-methylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-cyanonaphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(5-methyl-1,2,4-oxadiazol-3-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-(pyrimidin-2-yloxy)naphth-1-yl]-urea; *N*-[5-acetylnaphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-bromonaphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(6-methylpyridin-2-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(2-methylpyridin-5-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(2-methylpyridin-3-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-(pyrimidin-2-yl)naphth-1-yl]-urea; *N*-[5-bromonaphth-1-yl]-*N'*-[4-(piperazin-1-yl)quinolin-6-yl]-urea; 2,3-dihydro-8-(4-methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]pyrrolo[2,1-*b*]



g]quinoline; 2*J*-dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(5-methyl-1,2,4-oxadiazol-3-yl)naphth-1-ylaminocarbonyl]pyrrolo[2*J*-g]quinoline; 2*J*-dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]pyrrolo[2*J*-g]quinoline; 9-(4-methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-*g*]quinoline; 9-(4-methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-*g*]quinoline; *N*-[8-bromoquinolin-4-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[8-(2-fluorophenyl)quinolin-4-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[8-(2-methoxyphenyl)quinolin-4-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2-biphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2*J*-dichlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N'*-[4-biphenyl]-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3,4-dichlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-chlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3-cyanophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[4-phenoxyphenyl]-urea; *N*-[4-bromophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-acetylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2-bromophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3,5-bis(trifluoromethyl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3-acetylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2,6-difluorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3-bromophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[naphth-1-yl]-urea; *N*-[2,6-dichlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-chloro-2-methylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-bromo-3-methylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-2-nitrophenylacetamide; 4-bromo-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-4-biphenylacetamide; 3,4-dichloro-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]benzamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-2-ylacetamide; 4-dimethylamino-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; 3,4-difluoro-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; *N*-[4-(4-methylpiperazin-1-

yl)quinolin-6-yl]-3-phenoxyphenylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylcarboxamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-4-phenoxybenzamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-oxoindan-2-yl]-urea; 2,3-dihydro-8-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]pyrrolo[2*J*-*g*]quinoline; 9-(4-methylpiperazin-1-yl)-1-[(5-oxo-5,6,7,8-tetrahydronaphth-6-yl)aminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-*g*]quinoline; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- BRL-15,572 (3-[4-(3-chlorophenyl)-1-piperazinyl]-1,1-diphenyl-2-propanol);
- LY-310762 (1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl}-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one);
- GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
- LY-393558 (1-{2-[4-(6-fluoro-1*H*-indol-3-yl)-3,6-dihydro-1(2*H*)-pyridinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide);
- methiothepin (1-methyl-4-[8-(methylsulfonyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl]piperazine);
- metergoline (benzyl{[(8β)-1,6-dimethylergolin-8-yl]methyl}carbamate);
- methysergide ((8β)-*N*-[(2*S*)-1-hydroxy-2-butanyl]-1,6-dimethyl-9,10-didehydroergoline-8-carboxamide);
- yohimbine (methyl(16α,17α)-17-hydroxyyohimban-16-carboxylate);
- ritanserine (6-(2-{4-[bis(4-fluorophenyl)methylene]-1-piperidinyl}ethyl)-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one);
- risperidone (3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)-1-piperidinyl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one);
- ziprasidone (5-{2-[4-(1,2-benzothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-1,3-dihydro-2*H*-indol-2-one); and
- pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- LY-310762 (1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl}-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one);
- 5 - GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
- LY-393558 (1-{2-[4-(6-fluoro-1*H*-indol-3-yl)-3,6-dihydro-1(2*H*)-pyridinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide);
- 10 - methiothepin (1-methyl-4-[8-(methylsulfonyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl]piperazine);
- metergoline (benzyl{[(8β)-1,6-dimethylergolin-8-yl]methyl}carbamate);
- methysergide ((8β)-*N*-[(2*S*)-1-hydroxy-2-butanyl]-1,6-dimethyl-9,10-didehydroergoline-8-carboxamide);
- 15 - yohimbine (methyl(16α,17α)-17-hydroxy-yohimban-16-carboxylate);
- ritanserine (6-(2-{4-[bis(4-fluorophenyl)methylene]-1-piperidinyl}ethyl)-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one);
- risperidone (3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)-1-piperidinyl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one);
- 20 - ziprasidone (5-{2-[4-(1,2-benzothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-1,3-dihydro-2*H*-indol-2-one); and
- pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- 25 - BRL-15,572 (3-[4-(3-chlorophenyl)-1-piperazinyl]-1,1-diphenyl-2-propanol);
- LY-310762 (1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl}-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one);
- GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);

- LY-393558 (1-{2-[4-(6-fluoro-1*H*-indol-3-yl)-3,6-dihydro-1(2*H*)-pyridinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide); and
  - pharmaceutically acceptable salts or esters thereof.
- 5 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:
- LY-310762 (1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl}-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one);
  - GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
  - 10 - LY-393558 (1-{2-[4-(6-fluoro-1*H*-indol-3-yl)-3,6-dihydro-1(2*H*)-pyridinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide); and
  - pharmaceutically acceptable salts or esters thereof.
- 15 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:
- BRL-15,572 (3-[4-(3-chlorophenyl)-1-piperazinyl]-1,1-diphenyl-2-propanol);
  - LY-310762 (1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl}-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one); and
  - 20 - pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- LY-310762 (1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl}-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one); and
- 25 - pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide); and

- pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- BRL-15,572 (3-[4-(3-chlorophenyl)-1-piperazinyl]-1,1-diphenyl-2-propanol);  
5 and
- pharmaceutically acceptable salts or esters thereof.

In a second embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is an antibody that blocks 5-HTR<sub>1D</sub> activation (*i.e.*, a 5-HTR<sub>1D</sub> blocking antibody). The 5-HTR<sub>1D</sub> blocking antibodies contemplated in the present invention may, for  
10 instance, impair the binding of 5-HT to the receptor by binding to said receptor.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is a polyclonal antibody, preferably a 5-HTR<sub>1D</sub> polyclonal blocking antibody.

Polyclonal antibodies can be produced by various procedures well-known in the art. For example, a host animal such as a rabbit, mouse, rat, *etc.*, can be immunized by injection  
15 with an antigen to induce the production of sera containing polyclonal antibodies specific for the antigen. The antigen can include a natural, synthesized, or expressed protein, or a derivative (*e.g.*, fragment) thereof. Various adjuvants may be used to increase the immunological response, depending on the host species, and include, but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide,  
20 surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacillus Calmette-Guérin) and *Corynebacterium parvum*. Such adjuvants are also well-known in the art. Antibodies can be purified from the host's serum.

25 In a preferred embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is a monoclonal antibody, preferably a 5-HTR<sub>1D</sub> monoclonal blocking antibody.

In particular, monoclonal antibodies can be prepared using hybridoma methods, including, but not limited to, the hybridoma technique originally described by Kohler and

Milstein (1975. *Nature*. **256(5517)**:495-7); the human B-cell hybridoma technique (Cote *et al.*, 1983. *Proc Natl Acad Sci U S A*. **80(7)**:2026-30); and the EBV-hybridoma technique (Cole *et al.*, 1985. *J Immunol Methods*. **78(2)**:271-8). Using the hybridoma method, a mouse, hamster, or any other appropriate host animal is immunized as  
5 described above to elicit the production by lymphocytes of antibodies that will specifically bind to an immunizing antigen. Lymphocytes can also be immunized *in vitro*. Following immunization, the lymphocytes are isolated and fused with a suitable myeloma cell line using, for example, polyethylene glycol, to form hybridoma cells that can then be selected away from unfused lymphocytes and myeloma cells. Hybridomas that  
10 produce monoclonal antibodies directed specifically against a chosen antigen as determined by immunoprecipitation, immunoblotting, or by an *in vitro* binding assay (e.g., radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA)) can then be propagated either in *in vitro* culture using standard methods (Goding J. W. (1986). *Monoclonal antibodies: Principles and practice* (2nd ed.). London: Academic Press) or  
15 *in vivo* as ascites tumors in an animal. The monoclonal antibodies can then be purified from the culture medium or ascites fluid.

Alternatively, monoclonal antibodies can be made using recombinant DNA methods, as described in US patents US4,816,567 and US4,946,778. The polynucleotides encoding a monoclonal antibody are isolated from mature B-cells or hybridoma cells, such as by RT-  
20 PCR using oligonucleotide primers that specifically amplify the genes encoding the heavy and light chains of the antibody, and their sequence is determined using conventional procedures. The isolated polynucleotides encoding the heavy and light chains are then cloned into suitable expression vectors, which when transfected into host cells such as *Escherichia coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells or myeloma  
25 cells that do not otherwise produce immunoglobulin protein, monoclonal antibodies are generated by the host cells. Also, recombinant monoclonal antibodies or antigen-binding fragments thereof of the desired species can be isolated from phage display libraries expressing CDRs of the desired species as described (McCafferty *et al.*, 1990. *Nature*. **348(6301)**:552-4; Clackson *et al.*, 1991. *Nature*. **352(6336)**:624-8; Marks *et al.*, 1991. *J Mol Biol*. **222(3)**:581-597).  
30

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is a humanized antibody, preferably a 5-HTR1<sub>D</sub> humanized blocking antibody.

In a third embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is an aptamer that can block 5-HTR1<sub>D</sub> activation.

- 5 Aptamers are a class of molecule that represents an alternative to antibodies in term of molecular recognition. Aptamers are oligonucleotide or oligopeptide sequences with the capacity to recognize virtually any class of target molecules with high affinity and specificity. Such ligands may be isolated through Systematic Evolution of Ligands by EXponential enrichment (SELEX) of a random sequence library, as described in
- 10 Tuerk *et al.* (1990, *Science*, **249**(4968):505-10). The random sequence library is obtainable by combinatorial chemical synthesis of DNA. In this library, each member is a linear oligomer, eventually chemically modified, of a unique sequence. Possible modifications, uses and advantages of this class of molecules have been reviewed in Jayasena (1999, *Clin Chem*, **45**(9):1628-50). Peptide aptamers consists of a
- 15 conformationally constrained antibody variable region displayed by a platform protein, such as *Escherichia coli*'s thioredoxin A, that are selected from combinatorial libraries by two hybrid methods (Colas *et al.*, 1996, *Nature*, **380**(6574):548-50). Then, after raising aptamers directed against 5-HTR1<sub>D</sub> as described above, the skilled man in the art can easily select those blocking 5-HTR1<sub>D</sub> activation.
- 20 In a fourth embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is a polynucleotide.

The terms “**polynucleotide**”, “**nucleotide sequence**”, “**nucleic acid**”, “**nucleic acid molecule**”, “**nucleic acid sequence**” and “**oligonucleotide**” refer to a series of nucleotide bases (also called “nucleotides”) in DNA and RNA, and mean any chain of two or more

25 nucleotides. The polynucleotides can be chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded.

The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, *e.g.*, to improve stability of the molecule, its hybridization parameters, *etc.* The antisense oligonucleotide may comprise a modified base moiety which is selected

from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil,  $\beta$ -D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil,  $\beta$ -D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid, 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, a thio-guanine and 2,6-diaminopurine.

A nucleotide sequence typically carries genetic information, including the information used by cellular machinery to make proteins and enzymes. These terms include double- or single-stranded genomic and complementary DNA, RNA, any synthetic and genetically manipulated polynucleotide, and both sense and antisense polynucleotides. This includes single- and double-stranded molecules, *i.e.*, DNA-DNA, DNA-RNA and RNA-RNA hybrids, as well as "protein nucleic acids" (PNAs) formed by conjugating bases to an amino acid backbone. This also includes nucleic acids containing carbohydrate or lipids.

Exemplary DNAs include, but are not limited to, single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), plasmid DNA (pDNA), genomic DNA (gDNA), complementary DNA (cDNA), antisense DNA, chloroplast DNA (ctDNA or cpDNA), microsatellite DNA, mitochondrial DNA (mtDNA or mDNA), kinetoplast DNA (kDNA), provirus, lysogen, repetitive DNA, satellite DNA, and viral DNA.

Exemplary RNAs include, but are not limited to, single-stranded RNA (ssRNA), double-stranded RNA (dsRNA), small interfering RNA (siRNA), messenger RNA (mRNA), precursor messenger RNA (pre-mRNA), small hairpin RNA or short hairpin RNA (shRNA), microRNA (miRNA), guide RNA (gRNA), transfer RNA (tRNA), antisense RNA (asRNA), heterogeneous nuclear RNA (hnRNA), coding RNA,



non-coding RNA (ncRNA), long non-coding RNA (long ncRNA or lncRNA), satellite RNA, viral satellite RNA, signal recognition particle RNA, small cytoplasmic RNA, small nuclear RNA (snRNA), ribosomal RNA (rRNA), Piwi-interacting RNA (piRNA), polyinosinic acid, ribozyme, flexizyme, small nucleolar RNA (snoRNA), spliced leader  
5 RNA, viral RNA, and viral satellite RNA.

Polynucleotides described herein may be synthesized by standard methods known in the art, *e.g.*, by use of an automated DNA synthesizer (such as those that are commercially available from Biosearch, Applied Biosystems, *etc.*). A number of methods have been developed for delivering antisense DNA or RNA to cells, *e.g.*, antisense molecules can  
10 be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systemically. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be  
15 incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines. However, it is often difficult to achieve intracellular concentrations of the antisense sufficient to suppress translation of  
20 endogenous mRNAs. Therefore, a preferred approach utilizes a recombinant DNA construct in which the antisense oligonucleotide is placed under the control of a strong promoter. The use of such a construct to transfect target cells in the patient will result in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous target gene transcripts and thereby  
25 prevent translation of the target gene mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid,  
30 viral, or others known in the art, used for replication and expression in mammalian cells. Expression of the sequence encoding the antisense RNA can be by any promoter known

in the art to act in mammalian, preferably human, cells. Such promoters can be inducible or constitutive. Any type of plasmid, cosmid, yeast artificial chromosome, or viral vector can be used to prepare the recombinant DNA construct that can be introduced directly into the tissue site.

- 5 The polynucleotides may be flanked by natural regulatory (expression control) sequences or may be associated with heterologous sequences, including promoters, internal ribosome entry sites (IRES) and other ribosome binding site sequences, enhancers, response elements, suppressors, signal sequences, polyadenylation sequences, introns, 5' - and 3' -non-coding regions and the like.
- 10 The nucleic acids may also be modified by many means known in the art. Non-limiting examples of such modifications include methylation, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, and internucleotide modifications, such as, for example, those with uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoroamidates, carbamates, *etc.*) and with charged linkages
- 15 (*e.g.*, phosphorothioates, phosphorodithioates, *etc.*). Polynucleotides may contain one or more additional covalently linked moieties, such as, for example, proteins (*e.g.*, nucleases, toxins, antibodies, signal peptides, poly-1-lysine, *etc.*), intercalators (*e.g.*, acridine, psoralen, *etc.*), chelators (*e.g.*, metals, radioactive metals, iron, oxidative metals, *etc.*), and alkylators. The polynucleotides may be derivatized by formation of a
- 20 methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Furthermore, the polynucleotides herein may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, isotopes (*e.g.*, radioactive isotopes), biotin and the like.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is a

25 polynucleotide which interferes with 5-HTR1<sub>D</sub> synthesis. In one embodiment, the synthesis of 5-HTR1<sub>D</sub> may be blocked at the transcriptional level. In one embodiment, the synthesis of 5-HTR1<sub>D</sub> may be blocked at the translational level.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is an antisense oligonucleotide. Antisense oligonucleotides, including antisense RNA

molecules and antisense DNA molecules, would act to directly block the translation of 5-HTR1<sub>D</sub> mRNA by binding thereto and thus preventing protein translation or increasing mRNA degradation, thus decreasing the level of 5-HTR1<sub>D</sub>, and subsequently, 5-HTR1<sub>D</sub> activity, in a cell. For example, antisense oligonucleotides of at least about 15 bases and  
5 complementary to unique regions of the mRNA transcript sequence encoding 5-HTR1<sub>D</sub> can be synthesized, *e.g.*, by conventional phosphodiester techniques and administered by, *e.g.*, intravenous injection or infusion.

Methods for using antisense techniques for specifically inhibiting gene expression of genes whose sequence is known are well-known in the art (see, *e.g.*, see US patents  
10 US5,981,732, US6,046,321, US6,107,091, US6,365,354, US6,410,323, US6,566,131 and US6,566,135).

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is a ribozyme.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of  
15 RNA. The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Engineered hairpin- or hammerhead-motif ribozyme molecules that specifically and efficiently catalyze endonucleolytic cleavage of 5-HTR1<sub>D</sub> mRNA sequences are thereby useful within the scope of the present invention. Specific ribozyme cleavage sites  
20 within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, which typically include the following sequences, GUA, GUU and GUC. Once identified, short RNA sequences of between about 15 and 20 ribonucleotides corresponding to the region of the target gene containing the cleavage site can be evaluated for predicted structural features, such as secondary structure, that  
25 can render the oligonucleotide sequence unsuitable. The suitability of candidate targets can also be evaluated by testing their accessibility to hybridization with complementary oligonucleotides, using, *e.g.*, ribonuclease protection assays.

Both antisense oligonucleotides and ribozymes useful as inhibitors of 5-HTR1<sub>D</sub> gene expression can be prepared by known methods. These include, without limitation,

techniques for chemical synthesis such as, *e.g.*, solid phase phosphoramidite chemical synthesis. Alternatively, asRNA molecules can be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding the RNA molecule. Such DNA sequences can be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Various modifications to the oligonucleotides according to the present invention can be introduced as a means of increasing intracellular stability and half-life. Possible modifications include but are not limited to the addition of flanking sequences of ribonucleotides or deoxyribonucleotides to the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2'-O-methyl rather than phosphodiesterase linkages within the oligonucleotide backbone.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor according to the present invention is an interference RNA (RNAi). The term RNAi, as used herein, include, without limitation, small interfering RNAs (siRNAs), small hairpin RNAs (shRNAs) and microRNAs (miRNAs), targeted to a 5-HTR1<sub>D</sub> transcript; as well as RNAi vectors whose presence within a cell results in the production of an siRNA, shRNA or miRNA targeted to the target 5-HTR1<sub>D</sub> transcript. Such siRNA, shRNA or miRNA comprises a portion of RNA that is complementary to a region of the target 5-HTR1<sub>D</sub> transcript. Essentially, the RNAi contemplated in the present invention downregulates expression of 5-HTR1<sub>D</sub> via RNA interference.

RNA interference is a multistep process and is generally activated by double-stranded RNA (dsRNA) that is homologous in sequence to the targeted 5-HTR1<sub>D</sub> gene. Introduction of long dsRNA into the cells of organisms leads to the sequence-specific degradation of homologous gene transcripts. The long dsRNA molecules are metabolized to small (*e.g.*, 21-23 nucleotide) interfering RNAs (siRNAs, shRNAs or miRNAs) by the action of an endogenous ribonuclease known as Dicer. The interfering RNAs bind to a protein complex, termed RNA-induced silencing complex (RISC), which contains a helicase activity and an endonuclease activity. The helicase activity unwinds the two strands of RNA molecules, allowing the antisense strand to bind to the targeted 5-HTR1<sub>D</sub> RNA molecule. The endonuclease activity hydrolyzes the 5-HTR1<sub>D</sub> RNA at the site where the antisense strand is bound. Therefore, RNAi is an antisense mechanism of

action, as a single stranded (ssRNA) RNA molecule binds to the target 5-HTR<sub>1D</sub> RNA molecule and recruits a ribonuclease that degrades the 5-HTR<sub>1D</sub> RNA.

Methods for selecting an appropriate dsRNA or dsRNA-encoding vector are well-known in the art for genes whose sequence is known (see, *e.g.*, Tuschl *et al.*, **1999**. *Genes Dev.* **13(24)**:3191-7; Elbashir *et al.*, **2001**. *Nature*. **411(6836)**:494-8; Hannon, **2002**. *Nature*. **418(6894)**:244-51; McManus & Sharp, **2002**. *Nat Rev Genet.* **3(10)**:737-47; McManus *et al.*, **2002**. *RNA*. **8(6)**:842-50; Brummelkamp *et al.*, **2002**. *Science*. **296(5567)**:550-3; US patents US6,573,099 and US6,506,559; and International patent applications WO1999032619, WO2001036646 and WO2001068836).

- 10 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention is an siRNA.

Exemplary siRNAs inhibiting 5-HTR<sub>1D</sub> include, but are not limited to, the siRNA purchased from Dharmacon used in the example section.

- 15 The term “identity”, when used in a relationship between the sequences of two or more polypeptides or of two or more polynucleotides, refers to the degree of sequence relatedness between polypeptides or polynucleotides, as determined by the number of matches between strings of two or more amino acid or nucleotide residues. “Identity” measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer
- 20 program (*i.e.*, “algorithms”). Identity of related polypeptides or polynucleotides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Lesk A. M. (**1988**). *Computational molecular biology: Sources and methods for sequence analysis*. New York, NY: Oxford University Press; Smith D. W. (1993). *Biocomputing: Informatics and genome projects*. San Diego, CA: Academic Press;
- 25 Griffin A. M. & Griffin H. G. (**1994**). *Computer analysis of sequence data, Part 1*. Totowa, NJ: Humana Press; von Heijne G. (**1987**). *Sequence analysis in molecular biology: treasure trove or trivial pursuit*. San Diego, CA: Academic press; Gribskov M. R. & Devereux J. (**1991**). *Sequence analysis primer*. New York, NY: Stockton Press; Carillo *et al.*, **1988**. *SIAM J Appl Math.* **48(5)**:1073-82. Preferred methods for determining

identity are designed to give the largest match between the sequences tested. Methods of determining identity are described in publicly available computer programs. Preferred computer program methods for determining identity between two sequences include the GCG program package, including GAP (Genetics Computer Group, University of Wisconsin, Madison, WI; Devereux *et al.*, **1984**. *Nucleic Acids Res.* **12(1 Pt 1)**:387-95), BLASTP, BLASTN, and FASTA (Altschul *et al.*, **1990**. *J Mol Biol.* **215(3)**:403-10). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul *et al.* NCB/NLM/NIH Bethesda, Md. 20894). The well-known Smith Waterman algorithm may also be used to determine identity.

In one embodiment, the 5-HTR1D inhibitor according to the present invention is polynucleotide for targeted gene editing.

Examples of gene editing methods contemplated in the present invention include, but are not limited to, transcription activator-like effector nucleases (TALEN)-based editing system, clustered regularly interspaced short palindromic repeats-Cas9 (CRISPR-Cas9), meganucleases, zinc-finger nucleases (ZFNs) and the like.

In one embodiment, any of the polynucleotide according to the present invention may be delivered *in vivo* alone or in association with a vector.

In its broadest sense, a "vector" is any vehicle capable of facilitating the transfer of the polynucleotides according to the present invention to the cells, and preferably to cells expressing 5-HTR1D and in a cell-specific manner. Preferably, the vector transports the nucleic acid to cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In general, the vectors useful in the invention include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources that have been manipulated by the insertion or incorporation of the polynucleotide according to the present invention.

Viral vectors are a preferred type of vector and include, but are not limited to, nucleic acid sequences from the following viruses: retrovirus, such as Moloney murine leukemia virus (MMLV), Harvey murine sarcoma virus, murine mammary tumor virus, and rouse

sarcoma virus; adenovirus, adeno-associated virus (AAV); SV40-type viruses; Polyoma viruses; Epstein-Barr viruses; papilloma viruses; Herpes virus; Vaccinia virus; Polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known in the art. Preferred viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with the gene of interest. Non-cytopathic viruses include retroviruses (*e.g.*, lentivirus), the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (*i.e.*, capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for the high-efficiency transduction of genes *in vivo*. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell lined with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided by Kriegler (1990. *Methods Enzymol.* **185**:512-27). Preferred viruses for certain applications are the adeno-viruses and adeno-associated viruses, which are double-stranded DNA viruses that have already been approved for human use in gene therapy. The adeno-associated virus can be engineered to be replication deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as, heat and lipid solvent stability; high transduction frequencies in cells of diverse lineages, including hemopoietic cells; and lack of superinfection inhibition thus allowing multiple series of transductions. Reportedly, the adeno-associated virus can integrate into human cellular DNA in a site-specific manner, thereby minimizing the possibility of insertional mutagenesis and variability of inserted gene expression characteristic of retroviral infection. In addition, wild-type adeno-associated virus infections have been followed in tissue culture for greater than 100 passages in the absence of selective pressure, implying that the adeno-associated virus genomic integration is a relatively stable event. The adeno-associated virus can also function in an extrachromosomal fashion. Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well known to those of skill in the art. See, *e.g.*, Sambrook J.,

Fritsch E. F. & Maniatis T. (1989). *Molecular cloning: A laboratory manual*. New York, NY: Cold Spring Harbor Laboratory Press. In the last few years, plasmid vectors have been used as DNA vaccines for delivering antigen-encoding genes to cells *in vivo*. They are particularly advantageous for this because they do not have the same safety concerns as with many of the viral vectors. These plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operatively encoded within the plasmid. Some commonly used plasmids include pBR322, pUC18, pUC19, pRC/CMV, SV40 and pBlueScript. Other plasmids are well-known to those of ordinary skill in the art. Additionally, plasmids may be custom-designed using restriction enzymes and ligation reactions to remove and add specific fragments of DNA. Plasmids may be delivered by a variety of parenteral, mucosal and topical routes. For example, the DNA plasmid can be injected by intramuscular, intradermal, subcutaneous, or other routes. It may also be administered by intranasal sprays or drops, rectal suppository and orally. It may also be administered into the epidermis or a mucosal surface using a gene-gun. The plasmids may be given in an aqueous solution, dried onto gold particles or in association with another DNA delivery system including but not limited to liposomes, dendrimers, cochleate and microencapsulation.

In a fifth embodiment, the 5-HTR<sub>1D</sub> inhibitor according to the present invention can be further identified by screening methods described in the state of the art.

The screening methods according to the present invention can be carried out according to known methods. The screening method may measure the binding of a candidate compound to 5-HTR<sub>1D</sub>, or to cells or membranes bearing 5-HTR<sub>1D</sub>, or a fusion protein thereof by means of a label directly or indirectly associated with the candidate compound. Alternatively, a screening method may involve measuring or, qualitatively or quantitatively, detecting the competition of binding of a candidate compound to 5-HTR<sub>1D</sub> with a labelled competitor (*e.g.*, antagonist or agonist). Further, screening methods may test whether the candidate compound results in a signal generated by an antagonist of the receptor, using detection systems appropriate to cells bearing the receptor. Antagonists can be assayed in the presence of a known agonist (*e.g.*, 5-HT) and an effect on activation by the agonist by the presence of the candidate compound is observed. Competitive



binding using known agonist such as 5-HT is also suitable. The antagonistic activity of compounds towards 5-HTR<sub>1D</sub> may be determined by using various methods well-known in the art. For example, 5-HTR<sub>1D</sub> antagonistic activity may be evaluated in a radioligand binding assay and in the 5-HT-induced von Bezold-Jarisch reflex (BJR) in rats, such as  
5 described by Turconi *et al.* (1990. *J Med Chem.* **33**(8):2101-8).

In one embodiment, the composition, pharmaceutical composition or medicament according to the present invention further comprises 5-hydroxytryptamine receptor 1B (5-HTR<sub>1B</sub>) inhibitor.

In one embodiment, 5-HTR<sub>1B</sub> inhibitors according to the present invention include, but  
10 are not limited to, small organic molecules, antibodies, aptamers and polynucleotides.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is a selective 5-HTR<sub>1B</sub> inhibitor. By “**selective**”, it is meant that the affinity of the inhibitor for 5-HTR<sub>1B</sub> is at least 2-fold, 5-fold, 10-fold, 15-fold, 20-fold, 25-fold, 50-fold, 100-fold or more higher than the affinity for the other human 5-HT receptor (5-HTR<sub>1A</sub>, 5-HTR<sub>1C</sub>,  
15 5-HTR<sub>1D</sub>, 5-HTR<sub>1E</sub>, 5-HTR<sub>1F</sub>, 5-HTR<sub>2</sub>, 5-HTR<sub>3</sub>, 5-HTR<sub>4</sub>, 5-HTR<sub>5</sub>, 5-HTR<sub>6</sub>, 5-HTR<sub>7</sub>).

The affinity of a 5-HTR<sub>1B</sub> inhibitor may be quantified by measuring the activity of 5-HTR<sub>1B</sub> in the presence of a range of concentrations of said inhibitor in order to establish a dose-response curve. From that dose response curve, an IC<sub>50</sub> value may be deduced which represents the concentration of inhibitor necessary to inhibit 50% of the response  
20 to an agonist (*e.g.*, 5-HT) in defined concentration. The IC<sub>50</sub> value may be readily determined by the one skilled in the art by fitting the dose-response plots with a dose-response equation as described in De Lean A. & Rodbard D. (1979) *Kinetics of cooperative binding*. In: O’Brien R.D. (eds) *General Principles and Procedures. The Receptors (A Comprehensive Treatise)*, Vol. 1. Springer, Boston, MA. IC<sub>50</sub> values can be  
25 converted into affinity constant (K<sub>i</sub>) using the assumptions of Cheng & Prusoff (1973. *Biochem Pharmacol.* **22**(23):3099-108).

Accordingly, a selective 5-HTR<sub>1B</sub> inhibitor is a compound for which at least one of the ratios:

- (i) K<sub>i</sub>(5-HTR<sub>1-7</sub>)/K<sub>i</sub>(5-HTR<sub>1B</sub>), and/or

(ii)  $IC_{50}(5\text{-HTR1-7}\backslash 5\text{-HTR1B}):IC_{50}(5\text{-HTR1B})$ ,  
is above 2:1, 5:1, 10:1, 15:1, 20:1, 25:1, 50:1, 100:1 or above,  
wherein “5-HTR1-7\5-HTR1B” means all 5-HT receptors except 5-HTR1B,  
*i.e.*, 5-HTR1A, 5-HTR1C, 5-HTR1D, 5-HTR1E, 5-HTR1F, 5-HTR2, 5-HTR3, 5-HTR4,  
5 5-HTR5, 5-HTR6 and 5-HTR7.

Accordingly, a selective 5-HTR1B inhibitor is a compound for which at least one of the ratios:

- (i)  $K_i(5\text{-HTR1D}):K_i(5\text{-HTR1B})$ , and/or  
(ii)  $IC_{50}(5\text{-HTR1D}):IC_{50}(5\text{-HTR1B})$ ,  
10 is above 2:1, 5:1, 10:1, 15:1, 20:1, 25:1, 50:1, 100:1 or above.

In a first embodiment, the 5-HTR1B inhibitor is a small organic molecule.

Exemplary 5-HTR1B inhibitors that are contemplated by the present invention include, but are not limited to, those described in US patents US6,197,773, US9,938,277, US6,509,340, US6,107,328, US6,346,622, US6,291,458, US7,101,881, US7,026,314,  
15 US6,747,030; US patent applications US20070010526, US20050085457, US20050171095, US20060025421, US20080318926; International patent applications WO1999029666 and WO1999031086; the content of all of which is hereby incorporated by reference.

Typically, 5-HTR1B inhibitors which may be contemplated by the present invention  
20 include, but are not limited to:

N-acyl and N-aroyl aralkyl amides derivatives such as the ones described in US patent 6,197,773; isoquinoline derivatives such as the ones described in US patent application 2007010526; ergoline compounds, such as the ones described in US patent 9,938,277; amide and urea derivatives, such as the ones described US patent  
25 6,509,340; benzanilide derivatives, such as the ones described in US patent 6,107,328; 2-substituted 1,2-benzisothiazole derivatives, such as the ones described in US patent 6,346,622; arylpiperazine and arylpiperidine derivatives such as the one described in international patent application WO9929666; quinolinepiperazine and quinolinepiperidine derivatives, such as the ones described in international patent

application WO9931086; 8-amino derivatives, such as the ones described in US patent application 2005085457 and US patent 7,026,314; morpholinobenzamide salts, such as the ones described in US Patent 6,291,458; tetrahydroquinoline derivatives, such as the ones described in US patent 7,101,881; piperazine derivatives, such as the ones described in US patent 6,747,030; pyridyl piperazine derivatives such as the ones described in US patent application 2006025421; aminomethylpyridyloxymethyl/benzisoxazole substituted azabicyclic compounds, such as the ones described in US patent application 20083118926; which are incorporated by reference.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US5,965,575, including, without limitation, *N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-yl-*N*-2-(indan-1-yl)ethylamine; *N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-yl-*N*-(indan-1-yl-methyl)amine; *N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-yl-*N*-3-(indan-1-yl)-propylamine; *N*-(benzocyclobuten-1-ylmethyl)-*N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylamine; *N*-3-(benzocyclobuten-1-yl)propyl-*N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylamine; *N*-2-(benzocyclobuten-1-yl)ethyl-*N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylamine; *N*-4-(benzocyclobuten-1-yl)butyl-*N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylamine; *N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-yl-*N*-(4,5-dimethoxybenzocyclobuten-1-ylmethyl)amine; *N*-2-(adamant-1-yl)ethyl-*N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylamine; *N*-adamant-1-ylmethyl-*N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylamine; 5,6-dihydro-8,9-dimethoxy-2-{2-[1-(2,3-dihydro[1,4]benzodioxin-5-yl)-piperid-4-ylaminoethyl]}pyrrolo[2,1-*a*]isoquinoline; 5,6-dihydro-2-{2-[1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylaminoethyl]}pyrrolo[2,1-*a*]isoquinoline; 5,6-dihydro-9-methoxy-2-{2-[1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylaminoethyl]}pyrrolo[2,1-*a*]isoquinoline; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-{*N*-benzyl-2-(indan-1-yl)ethylamino}piperidine; 5,6-dihydro-8,9-dimethoxy-2-{1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylaminomethyl}pyrrolo[2,1-*a*]isoquinoline; *N*-2-(adamant-2-yl)ethyl-*N*-1-(2,3-dihydro[1,4]benzodioxin-5-yl)piperid-4-ylamine; *N*-2-(adamant-2-yl)ethyl-*N*-1-(chroman-8-yl)piperid-4-ylamine; 5,6-dihydro-8,9-dimethoxy-2-{2-[1-(chroman-8-yl)piperid-4-ylamino-ethyl]}pyrrolo[2,1-*a*]isoquinoline; 5,6-dihydro-

8,9-dimethoxy-2-{2-[1-(6-fluorochroman-8-yl)piperid-4-ylaminoethyl]pyrrolo[2,1-*a*]isoquinoline; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US5,968,954, including, without limitation, 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(indan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(indan-2-yl)-*N*-methylaminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(5,6-methylenedioxyindan-2-yl)amino-piperidine; 4-*N*-(indan-2-yl)amino-1-(thiochroman-8-yl)piperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(5,6-dimethoxyindan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(5-methylindan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(chloroindan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(5-methoxyindan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(5,6-dimethylindan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(5-trifluoromethylindan-2-yl)-aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(4,7-dimethoxyindan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-*N*-(5-fluoroindan-2-yl)aminopiperidine; 4-*N*-(indan-2-yl)-*N*-methylamino-1-(2,3-dihydro-1,4-dioxino[2,3-*b*]pyridin-8-yl)-piperidine; 1-(2,3-dihydro[1,4]benzoxathiin-5-yl)-4-(indan-2-ylamino)piperidine; 1-(chroman-8-yl)-4-(indan-2-ylamino)piperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-3-(indan-2-ylamino)pyrrolidine; 1-(6-fluorochroman-8-yl)-4-(indan-2-ylamino)piperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-(5-nitroindan-2-ylamino)piperidine; 1-(chroman-8-yl)-4-5-(1,2,4-triazol-4-yl)indan-2-ylaminopiperidine; 1-(chroman-8-yl)-4-(cyclopenta[*f*-2,1,3]benzoxadiazol-6-yl)aminopiperidine; 1-(chroman-8-yl)-4-(5-fluoroindan-2-yl)aminopiperidine; 1-(2,3-dihydrobenzofuran-7-yl)-4-(5-fluoroindan-2-yl)aminopiperidine; 1-(chroman-8-yl)-4-(5,6-methylenedioxyindan-2-yl)aminopiperidine; 1-(benzofuran-7-yl)-4-(5-fluoroindan-2-yl)aminopiperidine; 1-(chroman-8-yl)-4-(5-methoxyindan-2-yl)aminopiperidine; 1-(4-hydroxychroman-8-yl)-4-(5,6-methylenedioxyindan-2-yl)aminopiperidine; 1-(2,3-dihydro[1,4]benzodioxin-5-yl)-4-(indan-2-ylamino)-4-methylpiperidine; 1-(2,3-dihydro(1,4-benzodioxin-5-yl)-4-*N*-(5-hydroxyindan-2-yl)aminopiperidine; 1-(chroman-8-yl)-4-*N*-(5-hydroxyindan-2-yl)aminopiperidine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,066,644, including, without limitation, 1'-(2-hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 1'-(2-hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 1'-(2-dimethylaminoethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 1'-(2-methoxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,100,272, including, without limitation, 5-2'-methyl-4'-(2-oxo-1-pyrrolidinyl)biphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 1'-methyl-5-2'-methyl-4'-(2-oxo-1-piperidinyl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-4'-(4,5-dihydro-2-oxooxazol-3-yl)-2'-methylbiphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-(4'-acetamido-2'-methylbiphenyl-4-carbonyl)-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 1'-methyl-5-2'-methyl-4'-(2-thioxo-1-pyrrolidinyl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-4'-(1,1-dioxo-2,3,4,5-tetrahydroisothiazol-2-yl)-2'-methylbiphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-4'-(4,5-dihydro-2-oxoimidazol-1-yl)-2'-methylbiphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-4'-(4,5-dihydro-3-methyl-2-oxoimidazol-1-yl)-2'-methylbiphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 1'-methyl-5-2'-methyl-4'-(3-methyl-2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-4'-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-2'-methylbiphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-4'-(2,3-dihydro-1-oxoisindol-2-yl)-2'-methylbiphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-f]indole-3,4'-piperidine; 5-2,3'-dimethyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-

/]indole-3,4'-piperidine; 1'-methyl-5-4'-(2-oxo-1-pyrrolidinyl)-2'-trifluoromethylbiphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-2'-chloro-4'-(2-oxo-1-pyrrolidinyl)biphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-4-(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-methylbenzoyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-4-(1-acetyl-2,3-dihydroindol-5-yl)-3-methylbenzoyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-5-(2'-methyl-4'-(2-oxo-1*H*-pyrazin-1-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-ethyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-1'-*N*-propyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-isopropyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-*N*-butyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-cyclopropylmethyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-1'-cyclopropylmethyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-allyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-cyclopentyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 2,3,5,6,7,8-hexahydro-1'-methyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonylspirofuro[2,3-*g*]quinoline-3,4'-piperidine; 2,3,5,6,7,8-hexahydro-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonylspirofuro[2,3-*g*]quinoline-3,4'-piperidine; *cis*-2',6'-dimethyl isomer of 5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydro-1',2',6'-trimethylspirofuro[2,3-*f*]indole-3,4'-piperidine; 5-2'-methoxycarbonyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-2'-hydroxymethyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 5-2'-methoxymethyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-tert-butyl-5-2'-methyl-4'-(2-

oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 2,3-dihydro-1'-methyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonylspirofuro[3,2-*f*]indole-3,4'-piperidine; 5-2'-methyl-4'-(2-oxo-1-pyrrolidinyl)biphenyl-4-carbonyl-1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-5-2'-methyl-4'-(3-methyl-2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-isopropyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 2,3-dihydro-1'-methyl-5-2'-methyl-4'-(2-oxopyrrolidin-1-yl)biphenyl-4-carbonylspirofuro[3,2-*f*]indole-3,4'-piperidine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,107,328, including, without limitation, 4-(hydroxymethyl)-1-methyl-1,2,3,6-tetrahydropyridine; 4-(2-iodophenoxymethyl)-1-methyl-1,2,3,6-tetrahydropyridine; 2,3-dihydro-1'-methylspirobenzofuran-3,4'-piperidine; 2,3-dihydro-1'-methyl-5-nitrospirobenzofuran-3,4'-piperidine; 5-amino-2,3-dihydro-1'-methylspirobenzofuran-3,4'-piperidine; 6-(cyanomethyl)-2,3-dihydro-1'-methyl-5-nitrospirobenzofuran-3,4'-piperidine; 2,3-dihydro-1'-methylspirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; 1'-methyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospirofuro[2,3-*f*]indole-3,4'-piperidine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,159,962, including, without limitation, 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxy-phenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methyl-1-naphthyl)-1-piperazinyl)ethylthieno-[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxy-1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-

dimethylcarbamoyl-3-2-(4-(2-methylphenyl)-1-piperazinyl)ethylthieno[2,3-  
*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(3-tri-  
fluoromethylphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-  
methyl-6-dimethylcarbamoyl-3-2-(4-(2-chloro-phenyl)-1-piperazinyl)ethylthieno[2,3-  
5 *d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-pyrimidin-2-  
yl)piperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-  
dimethylcarbamoyl-3-2-(4-pyridin-2-yl)piperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-  
one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-quinolin-2-yl)piperazin-1-  
yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-  
10 (4-(3,5-dichlorophenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-  
5-methyl-6-dimethylcarbamoyl-3-2-(4-tetralin-5-yl)piperazin-1-yl)ethylthieno[2,3-  
*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-indan-4-  
yl)piperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-  
dimethylcarbamoyl-3-2-(4-(2-cyanophenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-  
15 4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-isoquinolin-4-yl)piperazin-1-  
yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-3-  
(4-pyrimidin-2-yl)piperazin-1-yl)propylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-  
methyl-6-dimethylcarbamoyl-3-2-(4-(2-methoxyphenyl)-1-piperidinyl)ethylthieno[2,3-  
*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2-  
20 methoxyphenyl)-3,4-dihydro-1-piperidinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-  
dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-naphth-1-yl)piperidin-1-  
yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-  
(4-(2-methoxy-1-naphthyl)-3,4-dehydro-1-piperidinyl)ethylthieno[2,3-*d*]pyrimidin-4-  
one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-naphth-1-yl-1,4-hexahydro-1,4-  
25 diazepin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-carbamoyl-3-  
2-(4-(1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-  
methyl-6-carbamoyl-3-2-(4-pyrimidin-2-yl-piperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-  
4-one; 3,4-dihydro-5-methyl-6-diethylcarbamoyl-3-2-(4-(2-methoxyphenyl)-1-  
piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-Dihydro-5-methyl-6-  
30 diethylcarbamoyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one;  
3,4-dihydro-5-methyl-6-diethylcarbamoyl-3-2-(4-pyrimidin-2-yl)piperazin-1-  
yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-



(4-quinazolin-4-ylpiperazin-1-yl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2,4-dimethoxyphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-(2,5-dimethylphenyl)-1-piperazinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; 3,4-dihydro-5-methyl-6-dimethylcarbamoyl-3-2-(4-naphth-1-yl-3,4-dehydro-1-piperidinyl)ethylthieno[2,3-*d*]pyrimidin-4-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,159,970, including, without limitation, (*R*)-*N*-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-8-(4-ethylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-5-ethyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-5-ethyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-(4-morpholinocarbonyl)benzamide; (*R*)-*N*-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinocarbonylbenzamide; (*R*)-*N*-5-bromo-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; *N*-5-bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-5-bromo-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-trifluoromethylbenzamide; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; *N*-(4-morpholinophenyl)-8-(4-methylpiperazinyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxamide; (*R*)-*N*-(4-morpholinophenyl)-8-(4-methylpiperazinyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxamide; (*S*)-*N*-(4-morpholinophenyl)-8-(4-methylpiperazinyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxamide; (*R*)-*N*-(morpholinocarbonylphenyl)-8-(4-methylpiperazin-1-yl)-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxamide; (*S*)-*N*-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl-4-morpholinobenzamide; (*S*)-*N*-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl-4-(4-piperidon-1-yl)benzamide; (*S*)-*N*-8-methyl-5-(4-methyl-piperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl-4-

(dimethylaminocarbonyl)benzamide; *N*-4-(4-morpholinyl)phenyl-8-methoxy-5-(4-methyl-piperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide; (*R*)-*N*-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-5-methoxy-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,197,773, including, without limitation, 3,4-dichloro-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 4-fluoro-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; *N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(1-methyl-2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(1-methyl-2-2-(4-methylpiperazin-1-yl)-phenyl-propyl)-benzamide; 3,4-dichloro-*N*-methyl-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; *N*-benzyl-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; *N*-(4-chlorobenzyl)-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(2-{2-methyl-(1-methylpyrrolidin-2-yl)methyl}-amino-phenyl)-ethyl)-benzamide; 3,4-dichloro-*N*-(2-2-(1-methyl-octahydro-pyrrolo[2,3-*c*]pyridin-6-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(2-2-(hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(2-2-(1-methylpiperidin-4-yl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(2-2-(2-dimethylaminoethoxy)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(2-2-(2-dimethylamino-ethylsulfanyl)-phenyl-ethyl)-benzamide; 3,4-dichloro-*N*-(2-2-(2-pyrrolidin-1-ylethoxy)-phenyl-ethyl)-benzamide; 4-chloro-*N*-(2-2-(3-dimethylamino-pyrrolidin-1-yl)-phenyl-ethyl)-benzamide; 4-chloro-*N*-(2-2-(2-methyl-(2-morpholin-4-yl-ethyl)-amino-phenyl)-ethyl)-benzamide; 2-(4-chlorophenyl)-*N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-acetamide; *N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-*N*-phenylacetamide; *N*-(2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl)-isonicotinamide; *N*-(2-2-(1-azabicyclo[2.2.2]oct-4-yl)-phenyl-ethyl)-*N*-methylbenzamide; *N*-(2-2-(1,4-dimethylpiperidin-4-yl)-phenyl-ethyl)-4-fluorobenzamide; 4-fluoro-*N*-(2-2-(9-methyl-3,9-diazabicyclo[3.3.1]non-3-yl)-phenyl-ethyl)-benzamide; *N*-(2-2-(1,4-diazabicyclo[3.3.1]non-4-yl)-phenyl-ethyl)-*N*-

- methylbenzamide; *N*-{1-methyl-2-2-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-phenyl-ethyl}-benzamide; 2,4-dichloro-*N*-methyl-*N*-{1-methyl-2-2-(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)-phenylethyl}-benzamide; *N*-{2-2-(4-methyloctahydroquinoxalin-1-yl)-phenyl-ethyl}-benzamide; *N*-{2-2-(1-ethylpyrrolidin-2-ylmethoxy)-phenyl-ethyl}-benzamide; 5-phenyloxazole-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-amide; 5-phenylthiophene-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-amide; 5-methylthiophene-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-amide; 4-fluoronaphthalene-1-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-amide; 5-fluoro-1*H*-indole-2-carboxylic acid{2-2-(4-methylpiperazin-1-yl)-phenyl-ethyl}-amide; 4-chloro-*N*-{2-2-(3,4,5-trimethylpiperazin-1-yl)-phenyl-ethyl}-benzamide; 3,4-dichloro-*N*-{2-2-(2,4,5-trimethylpiperazin-1-yl)-phenyl-ethyl}-benzamide; 3,4-dichloro-*N*-{2-2-(2,4,6-trimethylpiperazin-1-yl)-phenyl-ethyl}-benzamide; and pharmaceutically acceptable salts or esters thereof.
- 15 In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,291,458, including, without limitation, (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide hydrogen (2*S*,3*S*)-tartrate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide hydrogen (2*R*,3*R*)-tartrate; (*R*)-*N*-5-
- 20 methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide benzenesulfonate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide hydrogen 1,2-ethanedisulfonate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide hydrogen maleate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-
- 25 1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide hydrogen sulfate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide *D*-gluconate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide
- 30 methanesulfonate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide hydrogen (*S*)-maleate; (*R*)-*N*-5-methyl-8-(4-

- methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide  
 dihydrogen citrate; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-  
 naphthyl-4-morpholinobenzamide hydrochloride; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-  
 1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide *L*-lactate, (*R*)-*N*-5-methyl-  
 5 8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide  
 dihydrobromide; (*R*)-*N*-5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-  
 naphthyl-4-morpholinobenzamide monohydrobromide; (*R*)-*N*-5-methyl-8-(4-  
 methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-morpholinobenzamide  
 dihydrochloride; and pharmaceutically acceptable salts or esters thereof.
- 10 In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected  
 from those described in US6,346,622, including, without limitation, 3,3-dimethyl-2-3-(4-  
 (5-tetralinyl)-1-piperazinyl)prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide;  
 3,3-dimethyl-2-3-(4-(2-phenyl-4-quinazolinyl)-1-piperazinyl)prop-1-yl-2,3-dihydro-1,2-  
 benzoisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(2-quinolinyl)-1-piperazinyl)-prop-1-  
 15 yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-  
 diazepanyl)-prop-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-  
 (4-(4-chloro-1-phthalazinyl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-  
 1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-2-methyleneprop-1-yl-2,3-  
 dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(4-quinazolinyl)-1-  
 20 piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-  
 (4-(1-naphthyl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide;  
 3,3-dimethyl-2-2-(4-isoquinolin-4-yl)-1-piperazinyl)-eth-1-yl-2,3-dihydro-1,2-  
 benzoisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-prop-1-  
 yl-6-(1-pyrrolyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-  
 25 naphthyl)-1-piperazinyl)-prop-1-yl-6-benzoylamido-2,3-dihydro-1,2-benzisothiazole-  
 1,1-dioxide; 3,3-dimethyl-2-3-(4-(1-naphthyl)-1-piperazinyl)-prop-1-yl-6-nitro-2,3-  
 dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-(2,3-dimethylphenyl)-1-  
 piperazinyl)eth-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-2-(4-  
 (4-indanyl)-1-piperazinyl)-eth-1-yl-2,3-di-hydro-1,2-benzisothiazole-1,1-dioxide; 3,3-  
 30 dimethyl-2-3-(4-(4-chloro-1-naphthyl)-1-piperazinyl)prop-1-yl-2,3-dihydro-1,2-  
 benzoisothiazole-1,1-dioxide; 3,3-dimethyl-2-3-(4-(2-pyrimidinyl)-1-piperazinyl)-prop-

1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-(4-(4-methoxyphenyl)-1-piperazinyl)ethyl-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-(3-(4-(2-methoxyphenyl)-1-piperazinyl)-2-hydroxypropyl)-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-diethyl-2-(3-(4-(1-naphthyl)-1-piperazinyl)propyl)-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-(3-(4-(2,5-dimethylphenyl)-1-piperazinyl)propyl)-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-(4-(2-cyanophenyl)-1-piperazinyl)ethyl-1-yl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; 3,3-dimethyl-2-(4-(1-naphthyl)-1-piperazinyl)ethyl-1-yl-4-chloro-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,355,647, including, without limitation, 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-acetyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-benzyl-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-(4-chlorophenyl-2-ethyl)-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methyl-1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methoxy-1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-pyrimidin-2-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methoxyphenyl)-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-

(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-naphth-1-yl)hexahydro-1,4-diazepin-1-yl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-(2-methylphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one;

5 3,4,5,7-tetrahydro-3-2-(4-tetralin-5-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-indan-1-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-(2-methoxyphenyl)-3,4-dehydro-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-naphth-1-yl-1-piperidinyl)-ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-3-2-(4-(2-methoxy-1-naphthyl-3,4-dehydro-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(2,3-dimethylphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one;

15 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(2-chlorophenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-pyrimidin-2-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-pyridin-2-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-quinolin-2-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one;

20 3,4,5,7-tetrahydro-6-ethyl-3-2-(4-(2-methoxyphenyl)-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-ethyl-3-3-(4-pyrimidin-2-yl-1-piperazinyl)propylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-methyl-3-2-(4-(3-trifluoromethyl-phenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-methyl-3-2-(4-(2-cyano-phenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one;

25 3,4,5,7-tetrahydro-6-methyl-3-2-(4-isoquinolin-4-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-methyl-3-2-(4-naphth-1-yl-3,4-dehydro-1-piperidinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one;

30 3,4,5,7-tetrahydro-6-acetyl-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-acetyl-3-2-(4-(2-methyl-1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3-

$d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-benzyl-3-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-(4-nitrophenyl-2-ethyl)-3-2-(4-(1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-  
 5 (4-aminobenzyl)-3-2-(4-(2-methyl-1-naphthyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-methylphenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-chlorophenyl)-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-phenyl-1-piperidiny)ethylpyrrolo[3',4':4,5]thieno[2,3-  
 10  $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-naphth-1-yl-1-piperidiny)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-(2-naphth-1-yl-3,4-dehydro-1-piperidiny)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 3,4,5,7-tetrahydro-6-carbethoxy-3-3-(4-(2-cyanophenyl)-1-piperazinyl)propylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; 15 3,4,5,7-tetrahydro-6-carbethoxy-3-2-(4-indan-4-yl-1-piperazinyl)ethylpyrrolo[3',4':4,5]thieno[2,3- $d$ ]pyrimidin-4-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,509,340, including, without limitation, *N*-2-(5-fluoro-3-indolyl)ethyl-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenylurea; 4-(5-cyano-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(6-fluoro-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 3-{1-4-methoxy-3-(4-methyl-1-piperazinyl)phenylaminocarbonyl-4-piperidyl}indole-5-carboxamide; 4-(5-fluoro-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-2-(3-indolyl)ethyl-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(4-fluoro-3-indolyl)-*N*-4-methoxy-3-(4-methylpiperazin-1-yl)phenylpiperidine-1-carboxamide; 4-(7-methoxyindol-3-yl)piperidine-1-carboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-amide; 4-4-(5-fluoro-3-indolyl)butylpiperazine-1-carboxylic acid 4-methoxy-  
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3-(4-methylpiperazin-1-yl)phenylamide; 4-(5-cyanoindol-3-yl)-3,6-dihydro-2H-pyridine[*lacuna*]1-carboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenylamide; 3-(5-fluoroindol-3-yl)pyrrolidine-1-carboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenyl-amide; 4-(5-fluoroindol-3-yl)cyclohexanecarboxylic acid 4-methoxy-3-(4-methylpiperazin-1-yl)phenylamide; *N*-2-(5-hydroxy-3-indolyl)ethyl-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenylurea; *N*-{2-4-(6-fluoro-3-indolyl)piperidin-1-ylethyl}-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenyl-urea; *N*-4-(5-cyano-3-indolyl)butyl-*N'*-4-methoxy-3-(4-methyl-1-piperazinyl)phenylurea; 4-4-(5-cyano-3-indolyl)butylpiperazine-1-carboxylic acid 4-methoxy-3-(4-methyl-1-piperazinyl)-phenylamide; 4-(5-fluoroindol-3-yl)piperidine-1-carboxylic acid (2,3-dihydro-1'-methylspiro(benzofuran)-3,4-piperidin)amide; *N*-{2-4-(6-fluoro-3-indolyl)piperidin-1-ylethyl}-2,3-dihydro-1-methylspiro(benzofuran)-3,4-piperidinurea; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US6,747,030, including, without limitation, *cis*-5-methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[5-(6-methylpyridin-2-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[5-(2-methyloxazol-5-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-(2,3-dichlorobenzoyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[(3-nitrophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-6-methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]-1,2,3,4-tetrahydro-7-(3,4,5-trimethylpiperazin-1-yl)quinoline; *cis*-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2,3-dichlorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline; *cis*-1-[(3-chloro-2-fluorophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2,3-difluorophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2,3-dichlorophenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2,3-dichlorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-trifluoromethylphenyl)acetyl]-5-



methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(3-chloro-2-fluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2,3-difluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthylacetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-chloro-1-[4-(6-methylpyridin-2-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[4-(2,6-dimethylpyridin-3-yl)-1-naphthoyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[4-(3,6-dimethylpyrazin-2-yl)-1-naphthoyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-chloro-3-fluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-bromo-3-fluorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-bromo-3-chlorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline; *cis*-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline; *cis*-1-[(3-chloro-2-fluorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline; *cis*-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(3-fluoro-2-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(3-chloro-2-cyanophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-acetyl-3-chlorophenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(3-bromo-2-methylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(3-cyano-2-methylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-bromo-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-acetyl-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[(2-phenyl-3-(trifluoromethyl)pyrazol-4-ylcarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-1-[(4-(2,5-dimethylpyridin-4-yl)benzoyl]-5-methoxyindoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[2'-methyl-4'-(2-

oxopyrrolidin-1-yl)biphenyl-4-carbonyl]indoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl]indoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoyl]-indoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-

5 (6-methylpyridin-2-yl)-1-naphthoyl]indoline; *cis*-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-5-cyano-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(3-aminocarbonyl-2-methylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[4-(1-methylpiperidin-4-yl)-1-naphthoyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[4-(piperidin-4-yl)-1-naphthoyl]-6-

10 (3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indole; *cis*-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indole; *cis*-1-(2,3-dichlorophenylaminocarbonyl)-5-methoxy-(3,4,5-trimethylpiperazin-1-yl)indole; *cis*-5-methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthylacetyl]-6-(3,4,5-

15 trimethylpiperazin-1-yl)indole; *cis*-1-[(3-chloro-2-fluorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindole; *cis*-1-[(2,3-dichlorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindole; *cis*-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indole; *cis*-5-methoxy-1-[4-(6-methylpyridin-2-yl)-1-naphthylaminocarbonyl]-6-(3,4,5-

20 trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[5-(6-methylpyridin-2-yl)-1-naphthylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[5-(2-methyloxazol-5-yl)-1-naphthylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-(2,3-dichlorophenylaminocarbonyl)-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-(3-chloro-2-fluorophenylaminocarbonyl)-5-

25 methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[3-fluoro-2-(trifluoromethyl)phenylaminocarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[2-chloro-3-(trifluoromethyl)phenylaminocarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[2-chloro-3-methylphenyl)amincarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[2-chloro-3-

30 (trifluoromethyl)phenyl)aminocarbonyl]-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-(2,3-dichlorophenylaminocarbonyl)-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-(2,3-dichlorophenylaminocarbonyl)-5-chloro-6-(3,4,5-

trimethylpiperazin-1-yl)indoline; *cis*-1-(2,3-dichlorophenylaminocarbonyl)-5-bromo-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-(2,3-dichlorophenylaminocarbonyl)-5-ethyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-5-methoxy-1-[2-(trifluoromethyl)phenylaminocarbonyl]-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-  
 5 [2-fluoro-3-(trifluoromethyl)phenylaminocarbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[2-chloro-3-(trifluoromethyl)phenylaminocarbonyl]-3,3-dimethyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-chloro-3-trifluoromethyl)phenoxy carbonyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2-chloro-3-trifluoromethylphenyl)acetyl]-6-(3,4,5-trimethylpiperazin-1-yl)indole; *cis*-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *cis*-1-[(2,3-dichlorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-methoxy-1-[4-(2-methyl-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)benzoyl]indoline; *cis*-1-[(3-chloro-2-fluorophenyl)acetyl]-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindole; *cis*-1-[(2-fluoro-3-trifluoromethylphenyl)acetyl]-5-fluoro-6-(3,4,5-trimethylpiperazin-1-yl)indole; *cis*-1-[2-chloro-3-(trifluoromethyl)phenyl]aminocarbonyl]-5-methyl-6-(3,4,5-trimethylpiperazin-1-yl)indoline; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US7,026,314, including, without limitation, 8-(4-methyl-1-piperazinyl)-*N*-[4-(4-morpholinyl)phenyl]-4-oxo-4*H*-chromene-2-carboxamide; 2-{1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one, 2-{1-[4-(1-acetyl-2,3-dihydro-1*H*-indol-6-yl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 2-chloro-5-(4-{1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-piperazin-1-yl)-benzonitrile; 2-{1-[4-(4-methoxyphenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-furan-2-yl-1*H*-pyrazol-3-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-imidazol-1-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-[1,2,3]thiadiazol-5-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid 4-

[1,2,3]thiadiazol-5-yl-benzylamide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2,5-diethoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-cyanomethyl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (1*H*-indol-5-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(2,6-dimethyl-morpholin-4-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-fluoro-phenoxy)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-2-(6-morpholin-4-yl-benzooxazol-2-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-hydroxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-ethoxy-benzothiazol-2-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-bromo-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 4-[4-({1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-

piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid  
 5 [4-(2,6-dimethyl-morpholin-4-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide;  
 10 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide;  
 15 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-dimethylsulfamoyl-piperazin-1-yl)-phenyl]-amide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid dimethylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid ethylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid cyclohexylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid cyclopentylamide;  
 25 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(1-pyrrolidin-1-yl-methanoyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(propane-2-sulfonyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-methyl-propanoyl)-piperazin-1-yl]-phenyl}-amide;  
 30 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-

carboxylic acid {4-[4-(1-morpholin-4-yl-methanoyl)-piperazin-1-yl]-phenyl}-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-  
 5 fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 10 carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-  
 15 amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-chloro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 20 carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-amide; 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-  
 25 piperazin-1-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-  
 30 amide; *N*-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-4-morpholin-4-yl-benzamide; 8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid(4-morpholin-4-yl-phenyl)-amide; (+)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-

morpholin-4-yl-phenyl)-amide; (-)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; racemic-8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (faster running isomer); 8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (slower running isomer); 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid ethylamide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-4-oxo-8-piperazin-1-yl-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-hydroxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid(4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 8-[(2-dimethylamino-ethyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[(3-dimethylamino-propyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*R*)-(+)-3-dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*S*)-(-)-3-dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-[methyl-(1-methyl-pyrrolidin-3-yl)-amino]-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[ethyl-(1-ethyl-pyrrolidin-3-yl)-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 4-dimethylamino-6-methoxy-8-(4-methyl-piperazin-1-

yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-4-methylamino-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-oxo-8-piperazin-1-yl-4H-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US7,101,881, including, without limitation, *N*-(4-chlorophenylacetyl)-8-(4-methylpiperazinyl)-tetrahydroisoquinoline; 3-(4-chlorophenyl)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-propan-1-one; 2-(4-methoxy-phenyl)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-*p*-tolyl-ethanone; 2-(4-chloro-phenoxy)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(2,4-dichloro-phenyl)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(2-chloro-phenyl)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-cyclopropyl-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-pyridin-3-yl-ethanone; (4-chloro-phenyl)-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; [8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-(4-morpholin-4-yl-phenyl)-methanone; 2-(3,4-dichloro-phenyl)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-chloro-benzenesulfonyl)-8-(4-methyl-piperazin-1-yl)-1,2,3,4-tetrahydroisoquinoline; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US7,109,201, including, without limitation, 1-acetyl-6-bromo-5-methoxyindoline; *cis*-1-acetyl-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline; 6-bromo-5-fluoroindoline; 1-acetyl-6-bromo-5-fluoroindoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-fluoroindoline; methyl-4-(6-acetamido-2-methylpyridin-3-yl)benzoate; methyl-4-[6-(methanesulfonamido)-2-methylpyridin-3-yl]benzoate; methyl-4-[6-(*N*-acetyl-*N*-methyl)amino-2-methylpyridin-



3-yl]benzoate; methyl-4-[6-(*N*-methanesulfonyl-*N*-methylanino)-2-methylpyridin-3-yl]benzoate; methyl-4'-acetamido-2'-methylbiphenyl-4-carboxylate; methyl-4'-(methanesulfonamido)-2'-methylbiphenyl-4-carboxylate; *cis*-5-chloro-6-(3,5-dimethylpiperazin-1-yl)indoline; *cis*-6-(3,5-dimethylpiperazin-1-yl)-5-methylindoline; 5 *cis*-1-acetyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; 5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline; *N*-[5-(4-{[6-[(3*R*,5*S*)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1*H*-indol-1-yl]carbonyl}phenyl)-6-methyl-2-pyridinyl]acetamide; *N*-[4'-({6-[(3*R*,5*S*)-3,5-dimethyl-1-piperazinyl]-5-fluoro-1*H*-indol-1-yl}carbonyl)-2-methyl-4-biphenyl]acetamide; and pharmaceutically acceptable salts  
10 or esters thereof.

In one embodiment, the at least one 5-HTR1B receptor inhibitor is selected from those described in US7,345,038: (7*R*,9*aS*)-*trans*-cyclohexyl-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine; (7*R*,9*aS*)-*trans*-2-(ethyl-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amino)-ethanol; 15 (7*R*,9*aS*)-*trans*-7-[6-(2,6-dimethyl-piperidin-1-ylmethyl)-pyridin-2-yloxymethyl]-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-1-(1-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-4-phenyl-piperidin-4-yl)ethenone; (7*R*,9*aS*)-*trans*-(1,2-dimethyl-propyl)-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyridol[1,2-*a*]pyrazin-7-ylmethoxyl-pyridin-2-ylmethyl}-amine; 20 (7*R*,9*aS*)-*trans*-cyclopropyl-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine; (7*R*,9*aS*)-*trans*-cyclopropylmethyl-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine; (7*R*,9*aS*)-*trans*-(4-chloro-benzyl)-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine; 25 (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; 30 (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(6-piperidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-

pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-dimethyl-amine;  
 (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-(tetrahydro-furan-2-ylmethyl)-amine; (7*R*,9*aS*)-  
 5 *trans*-7-[6-(2,5-dimethyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-(2,2,2-trifluoro-ethyl)-amine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-[3-(4-methyl-piperazin-1-yl)-propyl]-amine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-pyrrolidin-1-yl-amine; (7*R*,9*aS*)-*trans*-7-(6-azepan-1-ylmethyl-pyridin-2-yloxymethyl)-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazine;  
 10 (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(3-methyl-isoxazol-4-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-thiazol-2-yl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(3-methyl-isoxazol-5-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(3-methyl-pyridin-4-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(5-methyl-2*H*-pyrazol-3-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(5-methyl-pyridin-2-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(1*H*-pyrazol-3-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(6-methyl-pyridin-2-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-pyridin-2-yl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclopropylmethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-morpholin-4-yl-ethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-

octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-pyrimidin-4-yl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclopropyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(6-methoxy-pyridin-3-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-pyrrolidin-1-ylethyl)-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(4-methyl-[1.4]diazepan-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(tetrahydro-furan-2-ylmethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(1-phenylethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(1-phenylethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-pyridin-3-ylmethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-thiazol-2-yl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-thiazol-2-yl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(3-methyl-pyridin-4-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(5-methyl-2*H*-pyrazol-3-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(1*H*-pyrazol-3-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(6-methyl-pyridin-2-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-pyridin-2-yl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-cyclopropylmethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-

ylmethoxy)-pyridin-2-ylmethyl]-(2-morpholin-4-yl-ethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-pyrimidin-4-yl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(6-methoxy-pyridin-3-yl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(2-pyrrolidin-1-yl-ethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-diethyl-amine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-7-(5-azetidin-1-ylmethyl-pyridin-2-yloxymethyl)-2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-ethyl)-methyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclopentyl-methyl-amine; (7*R*,9*aS*)-*trans*-*N*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-*N,N'*-dimethylethane-1,2-diamine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methyl-aziridin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-7-(5-azepan-1-ylmethyl-pyridin-2-yloxymethyl)-2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methoxymethyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-*tert*-butyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-*tert*-butyl-methyl-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-thiazolidin-3-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-imidazol-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclohexyl-methyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-dimethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-

benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethyl-methyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-1-methyl-ethyl)-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(5-piperidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-dimethyl-amine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethyl-methyl-amine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclopentyl-methyl-amine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-ethyl)-methyl-amine; (7*S*,9*aS*)-*cis*-7-(5-azetidin-1-ylmethyl-pyridin-2-yloxymethyl)-2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methyl-aziridin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(2-methoxy-ethyl)-methyl-amine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-dimethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-cyclohexyl-methyl-amine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-cyclohexyl-methyl-amine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-dimethyl-amine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(2-methoxy-ethyl)-methyl-amine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(*R*)-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(*S*)-pyrrolidin-3-ol; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclohexyl-methyl-

amine; (7*S*,9*aS*)-*cis*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-pyrrolidin-(*S*)-3-ol; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-piperidin-4-ol; (7*S*,9*aS*)-*cis*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-pyrrolidin-(*R*)-3-ol; (7*R*,9*aS*)-*trans*-7-(5-azetidin-1-ylmethyl-pyridin-2-yloxymethyl)-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-3-ylmethyl}-dimethyl-amine; (7*R*,9*aS*)-*trans*-ethyl-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-3-ylmethyl}-methyl-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(6-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-benzyl-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(6-morpholin-4-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-morpholin-4-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-piperidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-diisopropyl-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-Benzo[*d*]isoxazol-3-yl-7-(6-morpholin-4-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(6-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(6-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(6-morpholin-4-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydro-

octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-(2-morpholin-4-yl-ethyl)-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(6-morpholin-4-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-piperidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-diethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-dimethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethyl-methyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-1-methyl-ethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-ethyl)-methyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclopentyl-methyl-amine; (7*R*,9*aS*)-*trans*-7-(5-azetidin-1-ylmethyl-pyridin-2-yloxymethyl)-2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methyl-aziridin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methoxymethyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-tert-butyl-amine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethyl-methyl-amine; (7*S*,9*aS*)-*cis*-7-(5-azetidin-1-ylmethyl-pyridin-2-yloxymethyl)-2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-dimethyl-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(2-methoxy-ethyl)-methyl-amine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(*S*)-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(*R*)-pyrrolidin-3-ol; (7*R*,9*aS*)-

*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxy-methyl]-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-piperidin-4-ol; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclohexyl-methyl-amine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(*S*)-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(*R*)-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(6-pyrrolidin-1-ylmethyl-pyridin-2-yloxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydro-pyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-benzyl-amine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxy-methyl)-octahydro-pyrido[1,2-*a*]pyrazine; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US7,479,559, including, without limitation, 3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-2-one; 4-{3-[2-(4-methyl-piperazin-1-yl)-benzyl]-2-oxo-pyrrolidin-1-yl}-benzoic acid ethyl ester; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(6-morpholin-4-yl-pyridin-3-yl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-morpholin-4-yl-phenyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclohexyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-ethyl-1-hydroxy-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[3-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(2-hydroxy-2-methyl-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-methoxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(2-methoxy-2-methyl-propyl)-phenyl]-3-



[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-methoxy-cyclobutyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-pyridin-4-yl-phenyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclohexyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-ethyl-1-hydroxy-propyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 3-[2-(4-ethyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-2-one; 3-[2-(2,5-dimethyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-pyrrolidin-2-one; 1-[6-(1-hydroxy-cyclopentyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[5-(1-hydroxy-1-methyl-ethyl)-pyridin-2-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[5-(1-hydroxy-cyclopentyl)-pyridin-2-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-2-one; (R)-4-{3-[2-(4-methyl-piperazin-1-yl)-benzyl]-2-oxo-pyrrolidin-1-yl}-benzoic acid ethyl ester; (R)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(6-morpholin-4-yl-pyridin-3-yl)-pyrrolidin-2-one; (R)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-morpholin-4-yl-phenyl)-pyrrolidin-2-one; (R)-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[4-(1-hydroxy-cyclohexyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[4-(1-ethyl-1-hydroxy-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[3-(1-Hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[4-(2-hydroxy-2-methyl-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-2-one; (S)-4-{3-[2-

(4-methyl-piperazin-1-yl)-benzyl]-2-oxo-pyrrolidin-1-yl}-benzoic acid ethyl ester; (S)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(6-morpholin-4-yl-pyridin-3-yl)-pyrrolidin-2-one; (S)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-morpholin-4-yl-phenyl)-pyrrolidin-2-one; (S)-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(1-hydroxy-cyclohexyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(1-ethyl-1-hydroxy-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[3-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(2-hydroxy-2-methyl-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US8,859,534, including, without limitation, *N,N*-dimethyl-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)-*N*-(pyridin-2-ylmethyl)benzofuran-2-carboxamide; *N*-(4-morpholinophenyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(1-phenylpiperidin-4-yl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(4-(methylsulfonyl)benzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-((1-methyl-1H-imidazol-4-yl)methyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(1-acetylpiperidin-4-yl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(1-(pyridin-2-yl)ethyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(1-(3-chloropyridin-2-yl)piperidin-4-yl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(4-cyanobenzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-methyl-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-cyclopropyl-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(3,3-difluorocyclobutyl)-7-(4-(2-(pyridin-2-

yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; azetidin-1-yl(7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-yl)methanone; (7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-yl)(pyrrolidin-1-yl)methanone; *N*-(4-(methylsulfonylmethyl)benzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(3-methoxyphenethyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-methyl-*N*-(3-(methylsulfonyl)benzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-((6-cyanopyridin-3-yl)methyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-methyl-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)-*N*-(pyridin-3-ylmethyl)benzofuran-2-carboxamide; *N*-(3-cyanobenzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; (7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-yl)(4-(thiazol-2-yl)piperazin-1-yl)methanone; *N*-(1-(3-methoxypyridin-2-yl)piperidin-4-yl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-methyl-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)-*N*-(pyridin-2-ylmethyl)benzofuran-2-carboxamide; *N*-(3-methoxybenzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(1-(pyridin-2-yl)cyclopropyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(4-methoxybenzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(2-(4-methylpyrimidin-2-yl)ethyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(2-(1-methyl-1*H*-imidazol-4-yl)ethyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)benzofuran-2-carboxamide; *N*-(1-(1-methyl-1*H*-pyrazol-5-yl)ethyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-(1-(6-methylpyridin-3-yl)ethyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; *N*-((2-methylpyrimidin-5-yl)methyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)-*N*-(pyridin-3-ylmethyl)benzofuran-2-carboxamide; (7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-yl)(3-(pyridin-3-yloxy)azetidin-1-yl)methanone; *N*-(3-hydroxybenzyl)-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(4-methoxypyridin-2-yl)ethyl)piperazin-1-yl)-*N,N*-dimethylbenzofuran-2-carboxamide; *N,N*-dimethyl-7-(4-(2-(5-methylpyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(4-cyanopyridin-2-yl)ethyl)piperazin-1-yl)-*N,N*-

dimethylbenzofuran-2-carboxamide; *N,N*-dimethyl-7-(4-(2-(6-(trifluoromethyl)pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(5-acetylpyridin-2-yl)ethyl)piperazin-1-yl)-*N,N*-dimethylbenzofuran-2-carboxamide; 7-(4-(2-(5-acetamidopyridin-2-yl)ethyl)piperazin-1-yl)-*N,N*-dimethylbenzofuran-2-carboxamide;

5 azetidin-1-yl(7-(4-(2-(6-methoxypyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-yl)methanone; 7-(4-(2-(6-methoxypyridin-2-yl)ethyl)piperazin-1-yl)-*N,N*-dimethylbenzofuran-2-carboxamide; 7-(4-(2-(5-fluoropyridin-2-yl)ethyl)piperazin-1-yl)-*N,N*-dimethylbenzofuran-2-carboxamide; 7-(4-(2-(3-methoxy-2-pyridyl)ethyl)piperazin-1-yl)-*N,N*-dimethylbenzofuran-2-carboxamide; 1-(5-(2-(4-(2-

10 (azetidine-1-carbonyl)benzofuran-7-yl)piperazin-1-yl)ethyl)indolin-1-yl)ethanone; 5-fluoro-*N,N*-dimethyl-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(1-acetylintolin-5-yl)ethyl)piperazin-1-yl)-5-fluoro-*N,N*-dimethylbenzofuran-2-carboxamide; 5-methoxy-*N,N*-dimethyl-7-(4-(2-(pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 4-bromo-*N,N*-dimethyl-7-(4-(2-

15 (pyridin-2-yl)ethyl)piperazin-1-yl)benzofuran-2-carboxamide; 7-(4-(2-(1-acetylintolin-5-yl)ethyl)piperazin-1-yl)-*N,N*-dimethylbenzofuran-2-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US9,938,277, including, without limitation, 3-((6*aR*,9*S*,10*aR*)-5-

20 cyclopropyl-7-methyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinolin-9-yl)-1,1-diethylurea; (6*aR*,9*R*)-5-cyclopropyl-*N*-((*S*)-1-hydroxybutan-2-yl)-4,7-dimethyl-4,6,6*a*,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (6*aR*,9*R*)-5-cyclopropyl-*N*-((*S*)-1-hydroxybutan-2-yl)-4,7-dimethyl-4,6,6*a*,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (6*aR*,9*R*,10*aS*)-*N*-((*S*)-1-hydroxybutan-2-yl)-10*a*-methoxy-

25 4,7-dimethyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (4*aR*,9*R*,10*aS*)-*N*-((*S*)-1-hydroxybutan-2-yl)-10*a*-methoxy-4,7-dimethyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide; (6*aR*,9*R*,10*aS*)-*N*-((*S*)-1-hydroxybutan-2-yl)-10*a*-methoxy-4,7-dimethyl-4,6,6*a*,7,8,9,10,10*a*-octahydroindolo[4,3-*fg*]quinoline-9-carboxamide; and pharmaceutically acceptable salts or esters thereof.

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In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20030064995, including, without limitation, *N*-[2-(5-fluoro-3-indolyl)ethyl]-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; 4-(5-cyano-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(6-fluoro-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 3-{1-[4-methoxy-3-(4-methyl-1-piperazinyl)phenylaminocarbonyl]-4-piperidyl}indole-5-carboxamide; 4-(5-fluoro-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-[2-(3-indolyl)ethyl]-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(4-fluoro-3-indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide; 4-(7-methoxyindol-3-yl)piperidine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; 4-[4-(5-fluoro-3-indolyl)butyl]piperazine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; 4-(5-cyanoindol-3-yl)-3,6-dihydro-2*H*-pyridine[*lacuna*]1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; 3-(5-fluoroindol-3-yl)pyrrolidine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; 4-(5-fluoroindol-3-yl)-cyclohexanecarboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide; *N*-[2-(5-hydroxy-3-indolyl)ethyl]-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; *N*-{2-[4-(6-fluoro-3-indolyl)piperidin-1-yl]ethyl}-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; *N*-[4-(5-cyano-3-indolyl)butyl]-*N'*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]urea; 4-[4-(5-cyano-3-indolyl)butyl]piperazine-1-carboxylic acid [4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]amide; 4-(5-fluoroindol-3-yl)piperidine-1-carboxylic acid (2,3-dihydro-1'-methylspiro(benzofuran)-3,4-piperidin) amide; *N*-{2-[4-(6-fluoro-3-indolyl)piperidin-1-yl]ethyl}-[2,3-dihydro-1-methylspiro(benzofuran)-3,4-piperidin]urea; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20040132720, including, without limitation, *cis-N*-[3-chloro-2-fluorophenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[2-fluoro-3-(trifluoromethyl)phenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[2,3-dichlorophenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-

3-carboxamide; *cis-N*-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]-5-(3,5-dimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[3-chloro-2-fluorophenyl]-6-fluoro-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[3-chloro-2-fluorophenyl]-5-(3,5-dimethylpiperazin-1-yl)-6-fluorobenzofuran-3-carboxamide; *cis-N*-[3-methyl-4-(6-methylpyridin-2-yl)phenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[3-methyl-4-(6-methylpyridin-2-yl)phenyl]-5-(3,4,5-trimethylpiperazin-1-yl)-6-fluorobenzofuran-3-carboxamide; *cis-N*-[4-(imidazol-1-yl)-3-methylphenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[4-(imidazol-1-yl)-3-methylphenyl]-6-fluoro-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[3-chloro-4-(pyridin-4-yl)phenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[3-chloro-4-(pyridin-4-yl)phenyl]-6-fluoro-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[4-(4-methoxycarbonylpiperazin-1-yl)-3-methylphenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[2-(4-cyanophenyl)-3-methylpyridin-5-yl]-6-fluoro-5-(3,4,5-trimethylpiperazin-1-yl)benzofuran-3-carboxamide; *cis-N*-[4-(4-methoxycarbonylpiperazin-1-yl)-3-methylphenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzothiophene-3-carboxamide; *cis-N*-[2,3-dichlorophenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzothiophene-3-carboxamide; *cis-N*-[4-(imidazol-2-yl)-3-methylphenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzothiophene-3-carboxamide; *cis-N*-[indol-5-yl]-5-(3,4,5-trimethylpiperazin-1-yl)benzothiophene-3-carboxamide; *cis-N*-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]-5-(3,4,5-trimethylpiperazin-1-yl)benzothiophene-3-carboxamide; *cis-N*-[2,3-dichlorophenyl]-5-(3,5-dimethylpiperazin-1-yl)benzothiophene-3-carboxamide; *cis-N*-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]-5-(3,5-dimethylpiperazin-1-yl)benzothiophene-3-carboxamide; *cis*-3-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carbonyl]-5-(3,4,5-trimethylpiperazin-1-yl)-1*H*-indole; *cis*-1-methyl-3-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carbonyl]-5-(3,4,5-trimethylpiperazin-1-yl)-1*H*-indole; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20050085457, including, without limitation, 8-(4-methyl-1-piperazinyl)-*N*-[4-(4-morpholinyl)phenyl]-4-oxo-4*H*-chromene-2-carboxamide; 2-{1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 2-{1-[4-(1-acetyl-2,3-dihydro-1*H*-indol-6-yl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 2-chloro-5-(4-{1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl)-piperazin-1-yl)-benzonitrile; 2-{1-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanoyl}-8-(4-methyl-piperazin-1-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-furan-2-yl-1*H*-pyrazol-3-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-imidazol-1-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-[1,2,3]thiadiazol-5-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid 4-[1,2,3]thiadiazol-5-yl-benzylamide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2,5-diethoxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-cyanomethyl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (1*H*-indol-5-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(2,6-dimethyl-morpholin-4-yl)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-fluoro-phenoxy)-phenyl]-amide; 8-(4-methyl-piperazin-1-yl)-2-(6-morpholin-4-yl-benzooxazol-2-yl)-chromen-4-one; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-hydroxy-4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (5-ethoxy-benzothiazol-2-yl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-

bromo-phenyl)-amide; 8-(4-methylpiperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 8-  
 5 (4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 4-[4-({1-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-  
 10 carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-  
 15 phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (2-methoxy-4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(2,6-dimethyl- morpholin-4-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-  
 20 yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl-methanoyl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-  
 25 cyano-4-morpholin-4-yl-phenyl)-amide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-  
 30 amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-dimethylsulfamoyl-piperazin-1-yl)-



phenyl]-amide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid dimethylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid ethylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid cyclohexylamide; 4-[4-({1-[6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid cyclopentylamide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(1-pyrrolidin-1-yl)-methanoyl]-piperazin-1-yl}-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-(4-(propane-2-sulfonyl)-piperazin-1-yl)-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(2-methyl-propanoyl)-piperazin-1-yl]-phenyl}-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-(4-(1-morpholin-4-yl)-methanoyl)-piperazin-1-yl}-phenyl}-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-chloro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-cyano-4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl)-methanoyl]-phenyl]-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(1-morpholin-4-yl)-methanoyl]-phenyl]-amide; 6-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (3-fluoro-4-morpholin-4-yl-phenyl)-amide; 6-chloro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-

carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-amide; 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester; 4-[4-({1-  
5 [6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-ethane sulfonyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-  
10 4*H*-chromene-2-carboxylic acid {4-[4-(3-hydroxy-propanoyl)-piperazin-1-yl]-phenyl}-amide; *N*-[8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-4-morpholin-4-yl-benzamide; 8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; (+)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; (-)-8-(4-methyl-piperazin-1-yl)-chroman-2-carboxylic  
15 acid (4-morpholin-4-yl-phenyl)-amide; racemic-8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (faster running isomer); 8-(4-methyl-piperazin-1-yl)-4-oxo-chroman-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide (slower running isomer); 4-[4-({1-[6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromen-2-yl]-methanoyl}-amino)-phenyl]-piperazine-1-carboxylic acid  
20 ethylamide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-ethoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-methoxy-4-oxo-8-piperazin-1-yl-4*H*-chromene-2-  
25 carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-hydroxy-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-[1,4]diazepan-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-  
30 1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-

- 1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 8-[(2-dimethylamino-ethyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[(3-dimethylamino-propyl)-methyl-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*R*)-(+)-3-dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-((3*S*)-(-)-3-dimethylamino-pyrrolidin-1-yl)-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-8-[methyl-(1-methyl-pyrrolidin-3-yl)-amino]-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 8-[ethyl-(1-ethyl-pyrrolidin-3-yl)-amino]-6-methoxy-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 4-dimethylamino-6-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-methoxy-4-methylamino-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-fluoro-4-oxo-8-piperazin-1-yl-4*H*-chromene-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; and pharmaceutically acceptable salts or esters thereof.
- In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20050165025, including, without limitation, *N*-[3-[3-(dimethylamino)ethoxy]-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-carboxamide; 1'-methyl-5-[(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine; 3-[3-dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide (*Z*)-4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)benzylidene]thiomorpholin-3-one; and pharmaceutically acceptable salts or esters thereof.
- In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20050282816, including, without limitation, 1-(4-tert-butylphenyl)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-ylmethyl)-

pyrrolidin-2-one; 3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(tetrahydropyran-4-yl)-phenyl]-pyrrolidin-2-one; 4-(4-tert-butylphenyl)-2-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-morpholin-3-one; 1-(4-tert-butylphenyl)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-

5 piperidin-2-one; 3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(tetrahydropyran-4-yl)-phenyl]-piperidin-2-one; 3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethylene)-piperidin-2-one; 3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-piperidin-2-one; 3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(4-methyl-tetrahydro-pyran-4-yl)-phenyl]piperidin-

10 2-one; (+)-1-(4-tert-butylphenyl)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-pyrrolidin-2-one; (+)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(tetrahydropyran-4-yl)-phenyl]-pyrrolidin-2-one; (+)-4-(4-tert-butylphenyl)-2-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-morpholin-3-one; (+)-1-(4-tert-butyl-phenyl)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-

15 3'-ylmethyl)-piperidin-2-one; (+)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(tetrahydropyran-4-yl)-phenyl]-piperidin-2-one; (+)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-piperidin-2-one; (+)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(4-methyltetrahydropyran-4-yl)-phenyl]piperidin-2-one; (-)-1-(4-tert-butylphenyl)-3-(4-methyl-3,4,5,6-tetrahydro-

20 2*H*-[1,2']bipyrziny-3'-ylmethyl)-pyrrolidin-2-one; (-)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(tetrahydropyran-4-yl)-phenyl]-pyrrolidin-2-one; (-)-4-(4-tert-butylphenyl)-2-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-morpholin-3-one; (-)-1-(4-tert-butyl-phenyl)-3-(4-methyl-3,4,5,6-tetrahydro-

25 2*H*-[1,2']bipyrziny-3'-ylmethyl)-piperidin-2-one; (-)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-piperidin-2-one; (-)-3-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrziny-3'-ylmethyl)-1-[4-(4-methyltetrahydropyran-4-yl)-phenyl]piperidin-2-one; and pharmaceutically acceptable salts or esters thereof.

30 In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20051710985, including, without limitation, 4-benzyl-2-[2-

(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorobenzyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-fluoro-6-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzyl]-thiomorpholin-3-one; 4-methyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(2-piperazin-1-ylbenzylidene)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-(4-piperazin-1-yl)-benzylidene)]-1-oxo thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-4-oxy-piperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 10-[4(3,4-dichlorophenyl)-3-oxo-thiomorpholin-2-yl]-2-methyl-3,4,2-dihydro-pyrazino[1,2-*a*]indol-2-ium; 4-benzyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,1-dioxothiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[3-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-5-trifluoromethyl-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-[4-(2-methoxyethyl)piperazin-1-yl]-benzylidene}thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-isopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-ethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-chloro-6-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-4-trifluoromethyl-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-oxo-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(5-fluoro-2-piperazin-1-yl-benzylidene)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[3,6-difluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-phenyl-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-phenyl-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(3,5-

dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-tert-butylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 3-[4-(3,4-dichlorophenyl)-3-oxo-thiomorpholin-2-ylidenemethyl]-6-dimethylamino-2-(4-methylpiperazin-1-yl)-benzonitrile; 4-(3,4-dichlorophenyl)-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-methyl-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[4-chloro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(2,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-(4-bromo-2-(4-methylpiperazin-1-yl)-benzylidene)-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(octahydropyrido[1,2-*a*]pyrazin-2-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-pyridin-3-yl-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-difluorophenyl)-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,5-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-methylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(2,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-4-(4-fluorophenyl)-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-4-phenylthiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-

[1,4]diazepan-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(2,4,6-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; (-)-3(*S*)-[[2-(4-methyl-1-piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-pyrrolidinone; enantiomeric mixture of (-)-3(*S*)-[[2-(4-methyl-1-piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-pyrrolidinone and (+)-3(*R*)-[[2-(4-methyl-1-piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-pyrrolidinone; 3,4-dichloro-*N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; 4-fluoro-*N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; *N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-(1-methyl-2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide; 3,4-dichloro-*N*-(1-methyl-2-[2-(4-methylpiperazin-1-yl)-phenyl]-propyl)-benzamide; 3,4-dichloro-*N*-methyl-*N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; *N*-benzyl-*N*-(2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide; *N*-(4-chlorobenzyl)-*N*-(2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide; 3,4-dichloro-*N*-2-{2-[methyl-(1-methylpyrrolidin-2-ylmethyl)-amino]-phenyl}-ethyl)-benzamide; 3,4-dichloro-*N*-{2-[2-(1-methyl-octahydro-pyrrolo[2,3-*c*]pyridin-6-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(1-methylpiperidin-4-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2-dimethylaminoethoxy)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2-dimethylamino-ethylsulfanyl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2-pyrrolidin-1-ylethoxy)-phenyl]-ethyl}-benzamide; 4-chloro-*N*-{2-[2-(3-dimethylamino-pyrrolidin-1-yl)-phenyl]-ethyl}-benzamide; 4-chloro-*N*-(2-{2-[methyl-(2-morpholin-4-yl-ethyl)-amino]-phenyl}-ethyl)-benzamide; 2-(4-chloro-phenyl)-*N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-acetamide; *N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-*N*-phenylacetamide; *N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-isonicotinamide; *N*-{2-[2-(1-azabicyclo[2.2.2]oct-4-yl)-phenyl]-ethyl}-*N*-methylbenzamide; *N*-{2-[2-(1,4-dimethylpiperidin-4-yl)-phenyl]-ethyl}-4-fluorobenzamide; 4-fluoro-*N*-{2-[2-(9-methyl-3,9-diazabicyclo[3.3.1]non-3-yl)-phenyl]-ethyl}-benzamide; *N*-(2-[2-(1,4-diazabicyclo[3.3.1]non-4-yl)-phenyl]-ethyl)-*N*-methylbenzamide; *N*-{1-methyl-2-[2-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-phenyl]-ethyl}-benzamide; 2,4-dichloro-*N*-methyl-*N*-{1-methyl-2-[2-(3-methyl-3,8-

diazabicyclo[3.2.1]oct-8-yl)-phenyl]-ethyl}-benzamide; *N*-{2-[2-(4-methyl-octahydroquinoxalin-1-yl)-phenyl]-ethyl}-benzamide; *N*-{2-[2-(1-ethylpyrrolidin-2-ylmethoxy)-phenyl]-ethyl}-benzamide; 5-phenyloxazole-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 5-phenylthiophene-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 5-methylthiophene-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 4-fluoronaphthalene-1-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 5-fluoro-1*H*-indole-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 4-chloro-*N*-{2-[2-(3,4,5-trimethylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2,4,5-trimethylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2,4,6-trimethylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20050182049, including, without limitation, 4-benzyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorobenzyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-fluoro-6-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzyl]-thiomorpholin-3-one; 4-methyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(2-piperazin-1-ylbenzylidene)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-(4-piperazin-1-yl)-benzylidene]-1-oxo-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-4-oxy-piperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 10-[4(3,4-dichlorophenyl)-3-oxo-thiomorpholin-2-yl]-2-methyl-3,4,2-dihydro-pyrazino[1,2-*a*]indol-2-ium; 4-benzyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,1-dioxothiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[3-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-5-trifluoromethyl-benzylidene]-



thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-[4-(2-methoxyethyl)piperazin-1-yl]-benzylidene}thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-isopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-ethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-chloro-6-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-4-trifluoromethyl-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-oxo-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(5-fluoro-2-piperazin-1-yl-benzylidene)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[3,6-difluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-phenyl-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-phenyl-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-tert-butylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 3-[4-(3,4-dichlorophenyl)-3-oxo-thiomorpholin-2-ylidenemethyl]-6-dimethylamino-2-(4-methylpiperazin-1-yl)-benzonitrile; 4-(3,4-dichlorophenyl)-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-methyl-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[4-chloro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(2,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-(4-bromo-2-(4-methylpiperazin-1-yl)-benzylidene)-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(octahydropyrido[1,2-*a*]pyrazin-2-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-pyridin-3-yl-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-

difluorophenyl)-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-  
 4-(3,5-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(2,5-  
 dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-  
 [2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-  
 5 dichlorophenyl)-2-[2-(3-methylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-  
 one; 4-(3,4-difluorophenyl)-2-[2-(2,4,5-trimethylpiperazin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(4-cyclopropylpiperazin-1-yl)-  
 benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-4-  
 (4-fluorophenyl)-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(2,5-  
 10 dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-  
 dimethylpiperazin-1-yl)-benzylidene]-4-phenylthiomorpholin-3-one; 4-(3,4-  
 dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-  
 (3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene]-  
 thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-  
 15 benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-  
 [1,4]diazepan-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-  
 (2,4,6-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-  
 cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one;  
 (-)-3(S)-[[2-(4-methyl-1-piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-  
 20 pyrrolidinone; enantiomeric mixture of (-)-3(S)-[[2-(4-methyl-1-  
 piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-pyrrolidinone and (+)-3(R)-  
 [[2-(4-methyl-1-piperazinyl)phenyl]methyl]-1-[4-(trifluoromethyl)phenyl]-2-  
 pyrrolidinone; 3,4-dichloro-*N*-(2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide;  
 4-fluoro-*N*-(2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide; *N*-(2-[2-(4-  
 25 methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide; 3,4-dichloro-*N*-(1-methyl-2-[2-(4-  
 methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide; 3,4-dichloro-*N*-(1-methyl-2-[2-(4-  
 methylpiperazin-1-yl)-phenyl]-propyl)-benzamide; 3,4-dichloro-*N*-methyl-*N*-(2-[2-(4-  
 methylpiperazin-1-yl)-phenyl]-ethyl)-benzamide; *N*-benzyl-*N*-(2-[2-(4-methylpiperazin-  
 1-yl)-phenyl]-ethyl)-benzamide; *N*-(4-chlorobenzyl)-*N*-(2-[2-(4-methylpiperazin-1-yl)-  
 30 phenyl]-ethyl)-benzamide; 3,4-dichloro-*N*-(2-{2-[methyl-(1-methylpyrrolidin-2-  
 yl)methyl]-amino}-phenyl)-ethyl)-benzamide; 3,4-dichloro-*N*-(2-[2-(1-methyl-  
 octahydro-pyrrolo[2,3-*c*]pyridin-6-yl)-phenyl]-ethyl)-benzamide; 3,4-dichloro-*N*-(2-[2-

(hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(1-methylpiperidin-4-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2-dimethylaminoethoxy)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2-dimethylamino-ethylsulfanyl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2-pyrrolidin-1-ylethoxy)-phenyl]-ethyl}-benzamide; 4-chloro-*N*-{2-[2-(3-dimethylamino-pyrrolidin-1-yl)-phenyl]-ethyl}-benzamide; 4-chloro-*N*-(2-{2-[methyl-(2-morpholin-4-yl-ethyl)-amino]-phenyl}-ethyl)-benzamide; 2-(4-chloro-phenyl)-*N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-acetamide; *N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-*N*-phenylacetamide; *N*-{2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-isonicotinamide; *N*-{2-[2-(1-azabicyclo[2.2.2]oct-4-yl)-phenyl]-ethyl}-*N*-methylbenzamide; *N*-{2-[2-(1,4-dimethylpiperidin-4-yl)-phenyl]-ethyl}-4-fluorobenzamide; 4-fluoro-*N*-{2-[2-(9-methyl-3,9-diazabicyclo[3.3.1]non-3-yl)-phenyl]-ethyl}-benzamide; *N*-(2-[2-(1,4-diazabicyclo[3.3.1]non-4-yl)-phenyl]-ethyl)-*N*-methylbenzamide; *N*-{1-methyl-2-[2-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-phenyl]-ethyl}-benzamide; 2,4-dichloro-*N*-methyl-*N*-{1-methyl-2-[2-(3-methyl-3,8-diazabicyclo[3.2.1]oct-8-yl)-phenyl]-ethyl}-benzamide; *N*-{2-[2-(4-methyloctahydroquinoxalin-1-yl)-phenyl]-ethyl}-benzamide; *N*-{2-[2-(1-ethylpyrrolidin-2-ylmethoxy)-phenyl]-ethyl}-benzamide; 5-phenyloxazole-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 5-phenylthiophene-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 5-methylthiophene-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 4-fluoronaphthalene-1-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 5-fluoro-1*H*-indole-2-carboxylic acid {2-[2-(4-methylpiperazin-1-yl)-phenyl]-ethyl}-amide; 4-chloro-*N*-{2-[2-(3,4,5-trimethylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2,4,5-trimethylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; 3,4-dichloro-*N*-{2-[2-(2,4,6-trimethylpiperazin-1-yl)-phenyl]-ethyl}-benzamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20050288304, including, without limitation, *N*-{8-[(2-dimethylamino-ethyl)-ethyl-amino]-5,6,7,8-tetrahydro-naphthalen-2-yl}-4-trifluoromethyl-benzamide; *N*-{8-[(2-dimethylamino-ethyl)-ethyl-amino]-5,6,7,8-

tetrahydro-naphthalen-2-yl}-4-fluoro-benzamide; 4-tert-butyl-*N*-{8-[(2-dimethylamino-ethyl)-ethyl-amino]-5,6,7,8-tetrahydro-naphthalen-2-yl}-benzamide; 1-[7-(4-benzyl-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-[7-(4-benzoyloxy-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-methyl-4-(7-phenyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-piperazine; 1-[7-(4-fluoro-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-[7-(3,5-dichloro-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-[7-(2-methoxy-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-methyl-4-[7-(4-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperazine; 1-[7-(3,4-dimethoxy-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-(7-biphenyl-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-[7-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid [1-(4-methoxy-phenyl)ethyl]-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 4-tert-butyl-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 4-trifluoromethyl-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid [2-(3-trifluoromethyl-phenyl)-ethyl]-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 4-chloro-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 4-fluoro-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (furan-2-ylmethyl)-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 2-chloro-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 3-trifluoromethyl-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 3-fluoro-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 2-methyl-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 2-methoxy-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 3-methoxy-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (2,5-dimethyl-2*H*-pyrazol-3-yl)-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (5-tert-butyl-2-methyl-

2*H*-pyrazol-3-yl)-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid [1-(4-chloro-phenylethyl)-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 3-chloro-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (pyridin-2-ylmethyl)-amide; 8-  
 5 (4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (4-chloro-phenyl)amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (5-methyl-[1,3,4]thiadiazol-2-yl)-amide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 3,4-difluoro-benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid 4-methoxy-  
 10 benzylamide; 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid pyridin-2-ylamide; 1-methyl-4-(7-*O*-tolyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-piperazine; 1-[7-(3,4-dichloro-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-[7-(3-methoxy-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 4-tert-butyl-*N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-benzamide; 2-methoxy-*N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-morpholin-4-yl-benzamide; 4-Isopropoxy-*N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-benzamide; 4-benzyloxy-*N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-benzamide; benzo[1,3]dioxole-5-carboxylic acid [8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-amide; 20 4-(cyclohex-1-enyloxy)-*N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-benzamide; *N*-{8-[(2-dimethylamino-ethyl)methyl-amino]-5,6,7,8-tetrahydro-naphthalen-2-yl}2-fluoro-4-morpholin-4-yl-benzamide; *N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-trifluoromethoxy-benzamide; 1-methyl-4-(7-pyridin-4-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-piperazine; 1-methyl-4-[7-(4-methyl-pyridin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperazine; 1-methyl-4-[7-(6-methyl-pyridin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperazine; 1-[7-(6-methoxy-pyridin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 1-methyl-4-(7-pyridin-2-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-piperazine; 4-{5-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-pyridin-2-yl}-morpholine; (+)-1-methyl-4-[7-(4-methyl-pyridin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperazine; (-)-1-methyl-4-[7-(4-methyl-pyridin-3-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperazine; 1-methyl-4-[6-(4-methyl-pyridin-3-yl)-chroman-4-yl]-piperazine; 1-methyl-4-(6-pyridin-4-yl-

- chroman-4-yl)-piperazine; 4-{5-[4-(4-methyl-piperazin-1-yl)-chroman-6-yl]-pyridin-3-yl}-morpholine; 1-[4-(4-methyl-piperazin-1-yl)-chroman-6-yl]-1*H*-pyrrolo[2,3-*b*]pyridine; 1-methyl-4-[6-(4-methyl-pyridin-3-yl)-chroman-4-yl]-piperazine; 1-methyl-4-[7-(4-trifluoromethyl-benzyloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperazine; 1-  
5 [7-(4-tert-butyl-benzyloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-4-methyl-piperazine; 6-morpholin-4-yl-nicotinic acid 8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl ester; *N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-6-morpholin-4-yl-nicotinamide; {4-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-ylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester; *N*-[8-(4-methyl-  
10 piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-trifluoromethyl-benzamide; *N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-trifluoromethyl-benzamide; 2-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-6-morpholin-4-yl-3,4-dihydro-2*H*-isoquinolin-1-one; 1-methyl-4-(7-piperidin-4-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-piperazine; 1-methyl-4-(7-piperidin-3-yl-1,2,3,4-  
15 tetrahydro-naphthalen-1-yl)-piperazine; 1-methyl-4-[7-(1-methyl-piperidin-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperazine; (5-fluoro-pyrimidin-2-yl)-{2-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-ethyl}amine; *N*-{2-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-ethyl}4-  
trifluoromethyl-benzamide; *N*-{2-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-ethyl}-4-trifluoromethyl-benzamide; {4-[8-(4-methyl-piperazin-1-  
20 yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}(4-trifluoromethyl-phenyl)-methanone; {3-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperidin-1-yl}(4-trifluoromethyl-phenyl)methanone; 4-aminomethyl-*N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-benzamide; (+)-1-methyl-4-(7-  
25 pyridin-4-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-piperazine; (-)-1-methyl-4-(7-pyridin-4-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)piperazine; 4-(1-hydroxy-1-methyl-ethyl)-*N*-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-benzamide; 3-[8-(4-methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl]-6'-morpholin-4-yl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl; and pharmaceutically acceptable salts or esters thereof.
- 30 In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20060025421, including, without limitation, 1-[4-(3,5-

dimethyl-isoxazol-4-yl)phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethylene]-piperidin-2-one; 2-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethylene]-4-[4-(tetrahydropyran-4-yl)-phenyl]-morpholin-3-one; 1-[4-(3,5-dimethylisoxazol-4-yl)phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 2-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-4-[4-(tetrahydropyran-4-yl)-phenyl]-morpholin-3-one; 1-[4-(2-methyloxazol-4-yl)-phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 1-[4-(2-tert-butyloxazol-4-yl)phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 1-[4-(2-isopropyl-oxazol-4-yl)phenyl]-3-[2-(4-methylpiperazin-1-yl)pyridin-3-ylmethyl]-piperidin-2-one; 1-[4-(2,5-dimethyloxazol-4-yl)-phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-[4-(tetrahydropyran-4-yl)-phenyl]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-[4-(tetrahydropyran-4-yl)-phenyl]-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-(4-oxazol-2-ylphenyl)-pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-(4-oxazol-4-ylphenyl)pyrrolidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-(4-oxazol-5-ylphenyl)-pyrrolidin-2-one; 1-[4-(2-methyloxazol-4-yl)phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-pyrrolidin-2-one; 1-[4-(1-methoxycyclobutyl)-phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-(4-trifluoromethylphenyl)-pyrrolidin-2-one; 1-[4-(1-hydroxycyclopentyl)phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methylethyl)-phenyl]-3-[2-(4-methylpiperazin-1-yl)pyridin-3-ylmethyl]-pyrrolidin-2-one; 1-(4-tert-butylphenyl)-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-pyrrolidin-2-one; 1-[4-(1-hydroxycyclopentyl)-phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 1-(4-tert-butylphenyl)-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-phenylpiperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-(4-trifluoromethoxyphenyl)-piperidin-2-one; 1-[4-(1-hydroxy-1-methylethyl)phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 1-[4-(1-hydroxycyclobutyl)-phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 1-(4-tert-butylphenyl)-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-

ylmethyl]-pyrrolidin-2-one; 1-(4-tert-butylphenyl)-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-piperidin-2-one; 3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-1-(4-tetrahydropyran-4-yl)-phenyl]-piperidin-2-one; 1-[4-(1-hydroxy-1-methylethyl)-phenyl]-3-[2-(4-methylpiperazin-1-yl)pyridin-3-ylmethyl]-piperidin-2-one; 1-[4-(1-hydroxy-1-methylethyl)phenyl]-3-[2-(4-methylpiperazin-1-yl)-pyridin-3-ylmethyl]-pyrrolidin-2-one; and pharmaceutically acceptable salts or ester thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20070010526, including, without limitation, 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-piperidin-1-ylmethyl-phenyl)-ethanone; 2-(4-isopropyl-phenyl)-1-[8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-methoxy-8-phenyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 1-[5-benzyloxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-isopropyl-phenyl)-ethanone; 1-[5-hydroxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-isopropyl-phenyl)-ethanone; 2-(4-isopropyl-phenyl)-1-(5-methoxy-8-pyridin-4-yl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanone; 2-(4-isopropyl-phenyl)-1-[5-methoxy-8-(1-methyl-1,2,3,6-tetrahydro-pyridinyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-6-propyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-propyl-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-propyl-benzenesulfonamide; *N*-isopropyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-tert-butyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-benzyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-(2-methoxy-benzyl)-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-(3-methoxy-benzyl)-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-(4-methoxy-benzyl)-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; 4-{2-[5-



methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-  
*H*-(2-methoxy-phenyl)-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-  
 yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*H*-(3-methoxy-phenyl)-  
 benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-  
 5 isoquinolin-2-yl]-2-oxo-ethyl}-*H*-(4-methoxy-phenyl)-benzenesulfonamide; *N*-  
 cyclopropyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-  
 2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N*-cyclobutyl-4-{2-[5-methoxy-8-(4-methyl-  
 piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; 4-  
 {2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-  
 10 ethyl}-benzenesulfonamide; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-  
 1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-methyl-benzenesulfonamide; 4-{2-[5-methoxy-8-  
 (4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-ethyl-  
 benzenesulfonamide; 4-{2-[*S*-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-  
 isoquinolin-2-yl]-2-oxo-ethyl}-*N,N*-dimethyl-benzenesulfonamide; *N*-ethyl-4-{2-[5-  
 15 methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-  
*N*-methyl-benzenesulfonamide; *N,N*-diethyl-4-{2-[*S*-methoxy-8-(4-methyl-piperazin-1-  
 yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzenesulfonamide; *N,N*-dipropyl-  
 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-  
 ethyl}-benzenesulfonamide; *N*-benzyl-4-{2-[*S*-methoxy-8-(4-methyl-piperazin-1-yl)-  
 20 3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-methyl-benzenesulfonamide; *N*-  
 benzyl-4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
 2-oxo-ethyl}-*N*-ethyl-benzenesulfonamide; *N*-benzyl-4-{2-[5-methoxy-8-(4-methyl-  
 piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-isopropyl-  
 benzenesulfonamide; 2-[4-(azetidine-1-sulfonyl)-phenyl]-1-[5-methoxy-8-(4-methyl-  
 25 piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-  
 piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-  
 ethanone; *N*-{2-[*S*-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-  
 yl]-2-oxo-ethyl}-isonicotinamide; *N*-{4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-isonicotinamide; *N*-{5-[5-methoxy-8-(4-  
 30 methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-  
 isonicotinamide; quinoline-5-carboxylic acid {2-[5-methoxy-8-(4-methyl-piperazin-1-  
 yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-amide; quinoline-5-carboxylic acid

{4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-amide; quinoline-5-carboxylic acid {5-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-amide; *N*-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzamide; *N*-{3-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-3-oxo-propyl}-benzamide; *N*-{4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-benzamide; *N*-{5-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-benzamide; 4-methoxy-*N*-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-benzamide; 4-methoxy-*N*-{4-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-4-oxo-butyl}-benzamide; 4-methoxy-*N*-{5-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-5-oxo-pentyl}-benzamide; (4-butylamino-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4-cyclohexyl-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4-benzyl-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4'-ethyl-biphenyl-4-yl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; (4'-hydroxy-biphenyl-4-yl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; [5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-(4-phenoxy-phenyl)-methanone; (4-benzoyl-phenyl)-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4-methoxy-phenylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-phenylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-methoxy-phenylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(3-methoxy-phenylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-benzylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-methoxy-benzylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(3-methoxy-benzylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-

3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4-methoxy-benzylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-propylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-isopropylsulfamoyl-phenyl)-amide;  
 5 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-cyclopropylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-tert-butylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-methylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-ethylsulfamoyl-phenyl)-amide;  
 10 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-cyclobutylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(thiazol-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-acetylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-butyrylsulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(methyl-phenyl-sulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(acetyl-methyl-sulfamoyl)-phenyl]-amide; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-morpholin-4-yl-phenyl)-ethanone;  
 15 2-(4-bromo-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-dimethylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(3-morpholin-4-yl-phenyl)-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-piperidin-1-yl-phenyl)-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-[4-(4-propyl-piperidin-1-yl)-phenyl]-ethanone; 2-{4-[4-(2-methoxy-ethyl)-piperidin-1-yl]-phenyl}-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-[4-(4-methyl-piperidin-1-yl)-phenyl]-ethanone; 2-[4-(4-

hydroxy-piperidin-1-yl)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-amino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-isopropyl-phenoxy)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-[4-(4-benzyl-piperazin-1-yl)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-isopropyl-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-thiomorpholin-4-yl-phenyl)-amide; 4-amino-*N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-butyramide; 2-(4-dibutylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-butylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-diphenethylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-phenethylamino-phenyl)-ethanone; 2-{4-[Bis-(2-benzyloxy-ethyl)-amino]-phenyl}-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-[4-(2-benzyloxy-ethylamino)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; biphenyl-4-yl-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-methanone; 2-biphenyl-4-yl-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-(5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl)-2-(4-methoxy-phenyl)-ethanone; 2-benzo[1,3]dioxol-5-yl-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(3,4-dimethoxy-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-fluoro-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-chloro-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-methyl-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-phenyl-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-

isoquinolin-2-yl]-2-(4-methylsulfanyl-phenyl)-ethanone; 2-(4-methanesulfinyl-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-methanesulfonamide; 2-[4-(2-methoxy-benzylamino)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-benzylamino-phenyl)-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-[4-(3-methoxy-benzylamino)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-[4-(4-methoxy-benzylamino)-phenyl]-1-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 2-(4-isopropyl-phenyl)-1-[5-methoxy-8-(4-methyl-piperazine-1-carbonyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3',4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-isopropyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-cyclohexyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(5-methoxy-pyrimidin-2-ylsulfamoyl)-phenyl]-amide; (4-{[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carbonyl]-amino)-benzyl)-phosphonic acid diethyl ester; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(3,4-dimethyl-isoxazol-5-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(6-methyl-benzothiazol-2-yl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-tert-butyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-sulfamoyl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-phenyl-2*H*-pyrazol-3-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(pyrrolidine-1-sulfonyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4,5-dimethyl-oxazol-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(2-phenyl-2*H*-pyrazol-3-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-

isoquinoline-2-carboxylic acid [4-(4-methyl-pyrimidin-2-ylsulfamoyl)-phenyl]-amide;  
 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid  
 [4-(2,6-dimethyl-pyrimidin-4-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-  
 piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(pyrimidin-2-  
 5 ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-  
 isoquinoline-2-carboxylic acid [4-(2,6-dimethoxy-pyrimidin-4-ylsulfamoyl)-phenyl]-  
 amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-  
 carboxylic acid [4-(6-methoxy-pyridazin-3-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-  
 (4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4,6-  
 10 dimethyl-pyrimidin-2-ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-  
 yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(6-methoxy-pyrimidin-4-  
 ylsulfamoyl)-phenyl]-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-  
 isoquinoline-2-carboxylic acid [4-(pyridin-2-ylsulfamoyl)-phenyl]-amide; 4-{2-[5-  
 methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-  
 15 benzoic acid methyl ester; 4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-  
 1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-*N*-methyl-benzamide; 8-(4-ethyl-piperazin-1-yl)-5-  
 methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-propylsulfamoyl-phenyl)-  
 amide; 8-(4-cyclohexyl-piperazin-1-yl)-5-methoxy-3,4-dihydro-1*H*-isoquinoline-2-  
 carboxylic acid (4-propylsulfamoyl-phenyl)-amide; 2-(4-isopropyl-phenyl)-1-(5-  
 20 methoxy-8-piperazin-1-yl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanone; *N*-(4-{2-[5-  
 methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-  
 phenyl)-2-phenyl-acetamide; *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-3-phenyl-propionamide; *N*-(4-{2-  
 [5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-  
 25 ethyl}-phenyl)-benzamide; *N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-benzenesulfonamide; 1-[5-  
 methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-(4-  
 phenylmethanesulfonyl-methyl-phenyl)-ethanone; 4-chloro-*N*-(4-{2-[5-methoxy-8-(4-  
 methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-  
 30 benzenesulfonamide; 4-tert-butyl-*N*-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-  
 dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-benzenesulfonamide; *N*-benzyl-*N*-  
 (4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-

- ethyl}-phenyl)-benzenesulfonamide; 1-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-3-(4-methoxy-phenyl)-urea; 1-(4-{2-[5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2-oxo-ethyl}-phenyl)-3-(3-methoxy-phenyl)-urea; [5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-[2'-methyl-4'-(5-methyl-[1,2,4]oxadiazol-3-yl)-biphenyl-4-yl]-methanone; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid (4-piperidin-1-yl-phenyl)-amide; 5-methoxy-8-(4-methyl-piperazin-1-yl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide; and pharmaceutically acceptable salts or esters thereof.
- 10 In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20070135442, including, without limitation, 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-yl)phenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-fluoro-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-
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yl)phenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 5 *N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-yl)phenyl)chroman-2-carboxamide; 10 (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-yl)phenyl)chroman-2-carboxamide; 15 (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-fluoro-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 20 *N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)chroman-2-carboxamide; 25 (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 30 (+)-6-methoxy-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-



carboxamide; 6-fluoro-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-fluoro-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-fluoro-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-*N*-(4-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)phenyl)-8-

(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-fluoro-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-*N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-fluoro-*N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-*N*-(4-(4-methyloxazol-2-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(4-methyloxazol-2-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-(4-methyloxazol-2-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-(2-methoxyethyl)piperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-(2-methoxyethyl)piperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-(2-methoxyethyl)piperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 8-(4-butylpiperazine-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-butylpiperazine-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-butylpiperazine-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-

8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide;  
5 (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide;  
10 6-methoxy-*N*-(4-morpholinophenyl)-8-(piperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(piperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(piperazin-1-yl)chroman-2-carboxamide; 6-methoxy-2-methyl-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-2-methyl-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide;  
15 (-)-6-methoxy-2-methyl-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-hydroxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-hydroxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-hydroxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide;  
20 (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2H)-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1-(2H)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide;  
25 (+)-6-fluoro-*N*-(4-(3-methyl-2-oxotetrahydropyrimidin-1(2H)-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxooxazolidin-3-yl)phenyl)chroman-2-carboxamide;  
30 (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxopyrrolidin-1-

yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(3-methyl-2,5-dioxoimidazolidin-1-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(2,5-dioxoimidazolidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(5-(methoxymethyl)-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-*N*-(4-(5-isopropyl-1,2,4-oxadiazol-3-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethoxypiperidin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-(4-methyloxazol-2-yl)phenyl)-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-(2-methoxyethyl)piperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-butylpiperazine-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(piperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-2-

methyl-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-hydroxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in US20070185107, including, without limitation, 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; *N*-(4-(4-acetylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-acetylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-acetylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-

carboxamide; *N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-(2-methoxyethyl)piperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-(2-methoxyethyl)piperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-(2-methoxyethyl)piperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-8-(piperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(piperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(piperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-

propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-

yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(4-



ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-

carboxamide; (-)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-

carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-

methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-

2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-

methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-

(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide;

yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (-)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; 8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-



carboxamide; (-)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (-)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; *N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-methylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-

6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-butylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-*N*-(4-morpholinophenyl)-8-(4-propylpiperazin-1-yl)chroman-2-carboxamide; (+)-8-(4-isopropylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide;  
 5 (+)-8-(4-ethylpiperazin-1-yl)-6-methoxy-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-  
 10 dimethylpiperazine-1-carboxamide; (+)-4-(4-(6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamido)phenyl)-*N,N*-dimethylpiperazine-1-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-methoxy-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-propanoylpiperazin-1-yl)phenyl)chroman-2-carboxamide;  
 15 (+)-*N*-(4-(4-ethanoylpiperazin-1-yl)phenyl)-6-methoxy-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected  
 20 from those described in US20080318926, including, without limitation, (7*R*, 9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(6-morpholin-4-ylmethylpyridin-2-yloxymethyl)-octahydropyrido[1,2-*a*]pyrazine; (7*R*, 9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-piperidin-1-ylmethylpyridin-2-yloxymethyl)-octahydropyrido[1,2-*a*]pyrazine; (7*R*, 9*aS*)-*trans*-2-(5-fluorobenzo[*d*]isoxazol-3-yl)-7-(5-pyrrolidin-1-ylmethylpyridin-2-yloxymethyl)-octahydropyrido[1,2-*a*]pyrazine; (7*R*, 9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-diethylamine;  
 25 (7*R*, 9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-dimethylamine; (7*R*, 9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethylmethylamine;  
 30 (7*R*, 9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-1-

methylethyl)-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxyethyl)-methylamine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclopentylmethylamine; (7*R*,9*aS*)-*trans*-7-(5-azetidin-1-ylmethylpyridin-2-yloxymethyl)-2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazine;  
5 (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methylaziridin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydropyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methoxymethylpyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydropyrido[1,2-*a*]pyrazine;  
10 (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-tert-butylamine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethylmethylamine; (7*S*,9*aS*)-*cis*-7-(5-azetidin-1-ylmethylpyridin-2-yloxymethyl)-2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-dimethylamine; (7*R*,9*aS*)-*trans*-cyclohexyl-{6-[2-(5-fluoro-benzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine;  
15 (7*R*,9*aS*)-*trans*-2-(ethyl-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amino)-ethanol; (7*R*,9*aS*)-*trans*-7-[6-(2,6-dimethylpiperidin-1-ylmethyl)-pyridin-2-yloxymethyl]-2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazine;  
20 (7*R*,9*aS*)-*trans*-(1,2-dimethylpropyl)-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(2-methoxyethyl)-methylamine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(*S*)-pyrrolidin-3-ol;  
25 (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(*R*)-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-[5-(2-methylpyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydropyrido[1,2-*a*]pyrazine;  
30 (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-piperidin-4-ol; (7*R*,9*aS*)-*trans*-cyclopropyl-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine;  
(7*R*,9*aS*)-*trans*-cyclopropylmethyl-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-

- octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine; (7*R*,9*aS*)-*trans*-2-(5-fluorobenzo[*d*]isoxazol-3-yl)-7-[6-(4-methylpiperazin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydropyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-2-(5-fluorobenzo[*d*]isoxazol-3-yl)-7-(6-piperidin-1-ylmethylpyridin-2-yloxymethyl)-octahydropyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-dimethylamine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-(tetrahydrofuran-2-ylmethyl)-amine; (7*R*,9*aS*)-*trans*-7-[6-(2,5-dimethylpyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-[3-(4-methylpiperazin-1-yl)-propyl]-amine; (7*R*, 9*aS*)-*trans*-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-pyrrolidin-1-ylamine; (7*R*,9*aS*)-*trans*-7-(6-azepan-1-ylmethylpyridin-2-yloxymethyl)-2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclohexyl-methyl-amine; (7*R*,9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(*S*)-pyrrolidin-3-ol; (7*R*, 9*aS*)-*trans*-1-[6-(2-benzo[*d*]isoxazol-3-yloctahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(*R*)-pyrrolidin-3-ol; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(6-pyrrolidin-1-ylmethylpyridin-2-yloxymethyl)-octahydropyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-[6-(2-benzo[*d*]isoxazol-3-yl-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-benzylamine; (7*R*,9*aS*)-*trans*-2-benzo[*d*]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethylpyridin-2-yloxymethyl)-octahydropyrido[1,2-*a*]pyrazine; (7*S*,9*aS*)-*cis*-2-benzo[*d*]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethypyridin-2-yloxymethyl)-octahydro-pyrido[1,2-*a*]pyrazine; (7*R*,9*aS*)-*trans*-6-(2-benzo[*d*]isoxazol-3-yloctahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-nicotinic acid methyl ester; (7*R*,9*aS*)-*trans*-6-(2-benzo[*d*]isoxazol-3-yloctahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-3-yl]-methanol; (7*R*,9*aS*)-*trans*-methanesulfonic acid 6-(2-benzo[*d*]isoxazol-3-yloctahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl ester; (7*R*,9*aS*)-*trans*-methanesulfonic acid 6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-

ylmethyl ester; (7*R*,9*aS*)-*trans*-6-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridine-2-carboxylic acid methyl ester; (7*R*,9*aS*)-*trans*-6-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-yl]-methanol; (7*R*,9*aS*)-*trans*-{6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridin-2-yl}-methanol; (7*R*,9*aS*)-*trans*-6-[2-(5-fluorobenzo[*d*]isoxazol-3-yl)-octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy]-pyridine-2-carboxylic acid ester; (7*R*,9*aS*)-*cis*-6-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridine-2-carboxylic acid methyl ester; (7*R*,9*aS*)-*cis*-6-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-yl]-methanol; (7*R*,9*aS*)-*cis*-methanesulfonic acid 6-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl ester; (7*R*,9*aS*)-*trans*-5-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridine-2-carboxylic acid methyl ester; (7*R*,9*aS*)-*trans*-[5-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-yl]-methanol; (7*R*,9*aS*)-*trans*-methanesulfonic acid 5-(2-benzo[*d*]isoxazol-3-yl)octahydropyrido[1,2-*a*]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl ester; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in WO1999029666, including, without limitation, 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline; 5-chloro-6-(4-ethylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline; 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-chloro-1-(9-oxo-9H-fluoren-2-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline; 5-chloro-1-(9-oxo-9H-fluoren-3-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline; 5-methoxy-6-(4-

methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline; 5-chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline; 5-bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline; 5-methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in WO1999031086, including, without limitation, *N*-[3-chloro-4-(pyridin-4-yl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[4-(pyridin-4-yl)naphth-1-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-(pyridin-4-yl)naphth-1-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-6-yl]-urea; 4-bromo-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide; 5-bromo-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-4-(pyridin-4-yl)naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-5-(pyridin-4-yl)naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]-urea; *N*-[3-cyano-4-(pyridin-4-yl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-5-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-8-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-3-yl]-urea; 2,6-dichloro-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; 5-(4-acetylphenyl)-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[quinolin-4-yl]-urea; *N*-[3-chloro-4-(pyridin-4-yl)phenyl]-*N'*-[4-(1-methylpiperidin-4-yl)quinolin-6-yl]-urea; *N*-[3-methyl-4-(6-methylpyridin-2-yl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(2,6-dimethylpyridin-4-yl)-3-methylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-cyanonaphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(5-methyl-1,2,4-oxadiazol-3-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-(pyrimidin-2-yloxy)naphth-1-yl]-urea; *N*-[5-acetylnaphth-1-yl]-

*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-bromonaphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(6-methylpyridin-2-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(2-methylpyridin-5-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[5-(2-methylpyridin-3-yl)naphth-1-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-(pyrimidin-2-yl)naphth-1-yl]-urea; *N*-[5-bromonaphth-1-yl]-*N'*-[4-(piperazin-1-yl)quinolin-6-yl]-urea; 2,3-dihydro-8-(4-methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]pyrrolo[2*J*-g]quinoline; 2*J*-dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(5-methyl-1,2,4-oxadiazol-3-yl)naphth-1-ylaminocarbonyl]pyrrolo[2*J*-g]quinoline; 2*J*-dihydro-8-(4-methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]pyrrolo[2*J*-g]quinoline; 9-(4-methylpiperazin-1-yl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-*g*]quinoline; 9-(4-methylpiperazin-1-yl)-1-[5-(pyrimidin-2-yloxy)naphth-1-ylaminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-*g*]quinoline; *N*-[8-bromoquinolin-4-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[8-(2-fluorophenyl)quinolin-4-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[8-(2-methoxyphenyl)quinolin-4-yl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2-biphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2*J*-dichlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N'*-[4-biphenyl]-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3,4-dichlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-chlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3-cyanophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[4-phenoxyphenyl]-urea; *N*-[4-bromophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-acetylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2-bromophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3,5-bis(trifluoromethyl)phenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3-acetylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[2,6-difluorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[3-bromophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[naphth-1-yl]-urea; *N*-[2,6-dichlorophenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-chloro-2-methylphenyl]-*N'*-[4-(4-

methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-bromo-3-methylphenyl]-*N'*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-2-nitrophenylacetamide; 4-bromo-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-4-biphenylacetamide; 3,4-dichloro-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]benzamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-2-ylacetamide; 4-dimethylamino-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; 3,4-difluoro-*N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]phenylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-3-phenoxyphenylacetamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]naphth-1-ylcarboxamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-4-phenoxybenzamide; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl]-urea; *N*-[4-(4-methylpiperazin-1-yl)quinolin-6-yl]-*N'*-[5-oxoindan-2-yl]-urea; 2,3-dihydro-8-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]pyrrolo[2*J*-g]quinoline; 9-(4-methylpiperazin-1-yl)-1-[(5-oxo-5,6,7,8-tetrahydronaphth-6-yl)aminocarbonyl]-1,2,3,4-tetrahydropyrido[2,3-*g*]quinoline; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in WO2006048727, including, without limitation, 1-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-3-(4-trifluoromethyl-phenyl)-1,3-dihydro-

imidazol-2-one; 1-(4-isopropoxy-phenyl)-3-{2-[2-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-ethyl}-1,3-dihydro-imidazol-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-{2-[3-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-ethyl}-1,3-dihydro-imidazol-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-3,4,5,6-tetrahydro-2*H*-[1,2']bipyrazinyl-3'-yl)-ethyl]-1,3-dihydro-imidazol-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-imidazolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-imidazolidin-2-one; 1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-tetrahydro-pyrimidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-1,3-dihydro-benzoimidazol-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-1,3-dihydro-imidazo[4,5-*b*]pyridin-2-one; 3-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-



ethyl}-7-phenyl-1*H*-quinazoline-2,4-dione; 5-tert-butyl-2-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-isoindole-1,3-dione; 2-[2-(4-methyl-piperazin-1-yl)-benzyl]-7-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one; 2-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-5-phenyl-2,3-dihydro-isoindol-1-one; 2-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-6-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one; 2-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-6-phenyl-1,2,3,4-tetrahydro-isoquinoline; 2-{2-[2-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-5-phenyl-2,3-dihydro-1*H*-isoindole; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in WO2007026219, including, without limitation, elzasonan; 3-(4-chlorobenzyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 3-(4-trifluoromethylphenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 3-(3,4-dichlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidin-4-one; 5-[2-(4-methylpiperazin-1-yl)-benzylidene]-2-phenylthiazolidin-4-one; 5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidine-2,4-dione; 3-(4-chlorophenyl)-2,2-dimethyl-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiazolidin-4-one; 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-imidazolidine-2,4-dione; 3-(4-chlorobenzyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-imidazolidine-2,4-dione; 4-benzyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorobenzyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-fluoro-6-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-morpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzyl]-thiomorpholin-3-one; 4-methyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(2-piperazin-1-ylbenzylidene)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-4-piperazin-1-yl)-benzylidene]-1-oxo-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-4-oxy-piperazin-1-yl)-benzylidene]-

thiomorpholin-3-one; 4-benzyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-1,1-dioxothiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[3-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-5-trifluoromethyl-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-[4-(2-methoxyethyl)piperazin-1-yl]-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-isopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-ethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-chloro-6-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-4-trifluoromethyl-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-(5-fluoro-2-piperazin-1-yl-benzylidene)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[3,6-difluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-phenyl-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-phenyl-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-tert-butylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 3-[4-(3,4-dichlorophenyl)-3-oxo-thiomorpholin-2-ylidenemethyl]-6-dimethylamino-2-(4-methylpiperazin-1-yl)-benzonitrile; 4-(3,4-dichlorophenyl)-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[5-methyl-2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[4-chloro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(2,4-difluorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[4-bromo-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(3,4,5-trimethylpiperazin-1-yl)-benzylidene]-

thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(octahydropyrido[1,2-*a*]pyrazin-2-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-pyridin-3-yl-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-difluorophenyl)-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,5-dichlorophenyl)-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,5-dichlorophenyl)-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-methylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-difluorophenyl)-2-[2-(2,4,5-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-4-(4-fluorophenyl)-thiomorpholin-3-one; 4-benzo[1,3]dioxol-5-yl-2-[2-(2,5-dimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(3,5-dimethylpiperazin-1-yl)-benzylidene]-4-phenylthiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(3-dimethylaminopyrrolidin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methyl-[1,4]diazepan-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(2,4,6-trimethylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 2-[2-(4-cyclopropylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 2-[2,4-dibromo-6-(4-methylpiperazin-1-yl)-benzylidene]-4-(3,4-dichlorophenyl)-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4]oxazepan-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4,5]oxadiazepan-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4]thiazepan-3-one; 4-(3,4-dichlorophenyl)-2-{2-[(2-dimethylaminoethyl)-methyl-amino]-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpiperidin-4-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1,4-dimethylpiperidin-4-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholine-3,5-dione; 4-(3,4-dichlorophenyl)-2-[2-(2-dimethylaminoethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(4-isopropylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-

- methylpyrrolidin-3-ylmethyl)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-[methyl-(1-methylpyrrolidin-2-ylmethyl)-amino]-benzylidene}-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-[2-(1-methylpyrrolidin-2-ylmethoxy)-benzylidene]-thiomorpholin-3-one; 4-(3,4-dichlorophenyl)-2-{2-[2-(1-methylpyrrolidin-2-yl)-ethyl]-benzylidene}-thiomorpholin-3-one; 1-(3,4-dichlorophenyl)-4-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperazin-2-one; 4-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-1-(4-trifluoromethylphenyl)-piperazin-2-one; 1-(4-chlorophenyl)-4-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperazin-2-one; 2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-morpholin-3-one; 2-[4-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[5-fluoro-2-(4-methylpiperazin-1-yl)-benzylidene]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-{1-[2-(4-methylpiperazin-1-yl)-phenyl]-ethylidene}-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 2-[2-(4-methylpiperazin-1-yl)-benzyl]-4-(4-trifluoromethylphenyl)-thiomorpholin-3-one; 4-(4-chlorophenyl)-6-methyl-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-thiomorpholin-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-[1,4]oxazepan-3-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-4*H*-[1,4]thiazin-3-one; 1-(4-chlorophenyl)-4,6,6-trimethyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperazin-2-one; 1-(4-chlorophenyl)-4-methyl-3-[2-(4-methylpiperazin-1-yl)-benzylidene]-piperazin-2-one; 4-(4-chlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzylidene]-morpholin-3-one; 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-oxazolidin-4-one; 3-(4-chlorophenyl)-2,2-dimethyl-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-imidazolidin-4-one; 3-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-benzylidene]-imidazolidin-4-one; and pharmaceutically acceptable salts or esters thereof.
- In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in WO2007026224, including, without limitation, 3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(6-morpholin-4-yl-pyridin-3-yl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-morpholin-4-yl-phenyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-

piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclohexyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-ethyl-1-hydroxy-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[3-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(2-hydroxy-2-methyl-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-methoxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(2-methoxy-2-methyl-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-methoxy-cyclobutyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-pyridin-4-yl-phenyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclohexyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-ethyl-1-hydroxy-propyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-(2-piperazin-1-yl-benzyl)-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzylidene]-pyrrolidin-2-one; 3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[5-methyl-2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[5-methyl-2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-piperidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-piperidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[5-methoxy-2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[5-methoxy-2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-fluoro-6-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(4-hydroxy-tetrahydro-pyran-4-yl)-phenyl]-3-[2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(4-hydroxy-tetrahydro-pyran-4-yl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-

piperidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-piperidin-2-one; 3-[5-fluoro-2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-piperidin-2-one; 3-[5-fluoro-2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-piperidin-2-one;  
5 one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(2-oxo-pyrrolidin-1-ylmethyl)-phenyl]-piperidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(3-oxo-1,3-dihydro-isobenzofuran-5-yl)-piperidin-2-one; 3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclobutyl)-phenyl]-piperidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(3-[1,3,4]oxadiazol-2-yl-phenyl)-pyrrolidin-2-one; 6-(1-hydroxy-1-methyl-ethyl)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-3,4,5,6-tetrahydro-[1,3']bipyridinyl-2-  
10 one; 3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-pyrrolidin-2-one; 3-[2-fluoro-6-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-pyrrolidin-2-one; 1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 6-(1-hydroxy-1-methyl-ethyl)-3-[2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-3,4,5,6-tetrahydro-[1,3']bi-pyridinyl-2-one;  
15 3-[5-fluoro-2-(3,4,5-trimethyl-piperazin-1-yl)-benzyl]-6'-(1-hydroxy-1-methyl-ethyl)-3,4,5,6-tetrahydro-[1,3']bipyridinyl-2-one; 3-[5-fluoro-2-(4-methyl-piperazin-1-yl)-benzyl]-6'-(1-hydroxy-1-methyl-ethyl)-3,4,5,6-tetrahydro-[1,3']bipyridinyl-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-[1,4]diazepan-1-yl)-benzyl]-pyrrolidin-2-one;  
20 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-[1,4]diazepan-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-(4-ethyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-2-one; 3-[2-(2,5-dimethyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-pyrrolidin-2-one;  
1-[6-(1-ethyl-1-hydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-pyrrolidin-2-one;  
25 1-[6-(1-hydroxy-cyclopentyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[5-(1-hydroxy-1-methyl-ethyl)-pyridin-2-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one;  
30 1-[5-(1-hydroxy-cyclopentyl)-pyridin-2-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-oxazol-4-yl-phenyl)-piperidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-

pyrazol-1-yl-phenyl)-piperidin-2-one; 1-[4-(2-methyl-oxazol-4-yl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-piperidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-oxazol-5-yl-phenyl)-piperidin-2-one; 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(morpholine-4-carbonyl)-phenyl]-pyrrolidin-2-one; 1-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one, 3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(piperidine-1-carbonyl)-phenyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-[2-(1-methyl-piperidin-4-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclohexyl)-phenyl]-3-[2-(1-methyl-piperidin-4-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(1-methyl-piperidin-4-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(1-methyl-piperidin-4-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-((3*R*,5*S*)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-((3*R*,5*S*)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[4-(4-hydroxy-tetrahydro-pyran-4-yl)-phenyl]-3-[2-((3*R*,5*S*)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; 1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-((3*R*,5*S*)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(6-morpholin-4-yl-pyridin-3-yl)-pyrrolidin-2-one; (*R*)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-morpholin-4-yl-phenyl)-pyrrolidin-2-one; (*R*)-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-1-[4-(2-hydroxy-2-methyl-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-1-[4-(1-methoxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-piperidin-2-one; (*R*)-3-[2-fluoro-6-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-pyrrolidin-2-one; (*R*)-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-((3*R*,5*S*)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-((3*R*,5*S*)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-1-[4-(4-hydroxy-tetrahydro-pyran-4-yl)-phenyl]-3-[2-((3*R*,5*S*)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*R*)-6'-(1-hydroxy-1-methyl-ethyl)-3-[2-(4-methyl-piperazin-

1-yl)-benzyl]-3,4,5,6-tetrahydro-[1,3']bipyridinyl-2-one; (R)-3-[2-fluoro-6-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-pyrrolidin-2-one; (R)-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-((3R,5S)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-3-[2-(4-ethyl-piperazin-1-yl)-benzyl]-1-  
5 [4-(1-hydroxy-1-methyl-ethyl-phenyl)-pyrrolidin-2-one; (R)-1-[6-(1-ethyl-1-hydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-pyrrolidin-2-one; (R)-1-[6-(1-hydroxy-cyclopentyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-  
10 [2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[5-(1-Hydroxy-cyclopentyl)-pyridin-2-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (R)-1-[4-(2-methyl-oxazol-4-yl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-piperidin-2-one; (R)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(piperidine-1-carbonyl)-phenyl]-pyrrolidin-2-one; (S)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(6-morpholin-4-yl-pyridin-3-yl)-pyrrolidin-2-one; (S)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-(4-morpholin-4-yl-phenyl)-pyrrolidin-2-one; (S)-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(2-hydroxy-2-methyl-propyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-  
20 pyrrolidin-2-one; (S)-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(1-methoxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-piperidin-2-one; (S)-3-[2-fluoro-6-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-pyrrolidin-  
25 2-one; (S)-1-[4-(1-hydroxy-cyclopentyl)-phenyl]-3-[2-((3R,5S)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-[2-((3R,5S)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-1-[4-(4-hydroxy-tetrahydro-pyran-4-yl)-phenyl]-3-[2-((3R,5S)-3,4,5-trimethyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (S)-6'-(1-hydroxy-1-methyl-ethyl)-3-[2-(4-methyl-piperazin-  
30 1-yl)-benzyl]-3,4,5,6-tetrahydro-[1,3']bipyridinyl-2-one; (S)-3-[2-fluoro-6-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-pyrrolidin-2-one; (S)-1-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-3-[2-((3R,5S)-3,4,5-trimethyl-



piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*S*)-3-[2-(4-ethyl-piperazin-1-yl)-benzyl]-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-pyrrolidin-2-one; (*S*)-1-[6-(1-ethyl-1-hydroxy-propyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*S*)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-pyrrolidin-2-one; (*S*)-1-[6-(1-hydroxy-cyclopentyl)-pyridin-3-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*S*)-1-[4-(1-hydroxy-cyclobutyl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*S*)-1-[5-(1-hydroxy-cyclopentyl)-pyridin-2-yl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-pyrrolidin-2-one; (*S*)-1-[4-(2-methyl-oxazol-4-yl)-phenyl]-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-piperidin-2-one; (*S*)-3-[2-(4-methyl-piperazin-1-yl)-benzyl]-1-[4-(piperidine-1-carbonyl)-phenyl]-pyrrolidin-2-one; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from those described in WO2007053093, including, without limitation, 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinoben-2-yl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinobenzyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinobenzyl)chroman-2-carboxamide; *N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (-)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; 6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (-)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)chroman-2-carboxamide; (+)-6-fluoro-8-(4-methylpiperazin-1-yl)-*N*-(4-morpholinobenzyl)chroman-2-carboxamide; (+)-*N*-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-6-fluoro-8-(4-methylpiperazin-1-yl)chroman-2-carboxamide; (+)-6-fluoro-8-

[illegible]

[illegible]

(methylsulfonyl)piperazin-1-yl)phenyl)chroman-2-carboxamide; and pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HT<sub>1B</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- 5 - SB-224289 ((1'-methyl-6,7-dihydro-5*H*-spiro[furo[2,3-*f*]indole-3,4'-piperidin]-5-yl)[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]methanone);
  - SB-216641 (*N*-{3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl}-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
  - AR-A000002 ((*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide);
  - 10 - GR-55562 (3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide);
  - NAS-181 ((2*R*)-2-({[3-(4-morpholinylmethyl)-2*H*-chromen-8-yl]oxy}methyl)morpholine methanesulfonate (1:2));
  - 15 - GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
  - LY-393558 (1-{2-[4-(6-fluoro-1*H*-indol-3-yl)-3,6-dihydro-1(2*H*)-pyridinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide);
  - 20 - alprenolol (1-(2-allylphenoxy)-3-(isopropylamino)-2-propanol);
  - oxprenolol (1-[2-(allyloxy)phenoxy]-3-(isopropylamino)-2-propanol);
  - isamoltane (1-(isopropylamino)-3-[2-(1*H*-pyrrol-1-yl)phenoxy]-2-propanol hydrochloride (1:1));
  - cyanopindolol (4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1*H*-indole-2-carbonitrile);
  - 25 - pindolol (1-(1*H*-indol-4-yloxy)-3-(isopropylamino)-2-propanol);
  - (S)-(-)-pindolol ((2*S*)-1-(1*H*-indol-4-yloxy)-3-(isopropylamino)-2-propanol);
  - carpindolol (4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1*H*-indole-2-carboxylic acid 1-methylethyl ester);
  - 30 - metergoline (benzyl{[(8β)-1,6-dimethylergolin-8-yl]methyl}carbamate);

- methiothepin (1-methyl-4-[8-(methylsulfanyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl]piperazine);
- yohimbine (methyl(16 $\alpha$ ,17 $\alpha$ )-17-hydroxy-yohimban-16-carboxylate);
- asenapine ((3*aS*,12*bS*)-5-chloro-2-methyl-2,3,3*a*,12*b*-tetrahydro-1*H*-  
5 dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrrole);
- methysergide ((8 $\beta$ )-*N*-[(2*S*)-1-hydroxy-2-butanyl]-1,6-dimethyl-9,10-didehydroergoline-8-carboxamide); and
- pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected  
10 from the group comprising or consisting of:

- SB-224289 ((1'-methyl-6,7-dihydro-5*H*-spiro[furo[2,3-*f*]indole-3,4'-piperidin]-5-yl)[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]methanone);
- SB-216641 (*N*-{3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl}-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
- 15 - AR-A000002 ((*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide);
- GR-55562 (3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide);
- NAS-181 ((2*R*)-2-({[3-(4-morpholinylmethyl)-2*H*-chromen-8-yl]oxy}methyl)morpholine methanesulfonate (1:2));
- 20 - GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
- LY-393558 (1-{2-[4-(6-fluoro-1*H*-indol-3-yl)-3,6-dihydro-1(2*H*)-pyridinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide);
- 25 - alprenolol (1-(2-allylphenoxy)-3-(isopropylamino)-2-propanol);
- oxprenolol (1-[2-(allyloxy)phenoxy]-3-(isopropylamino)-2-propanol);
- isamoltane (1-(isopropylamino)-3-[2-(1*H*-pyrrol-1-yl)phenoxy]-2-propanol hydrochloride (1:1));
- 30 - cyanopindolol (4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1*H*-indole-2-carbonitrile);

- pindolol (1-(1*H*-indol-4-yloxy)-3-(isopropylamino)-2-propanol);
- (S)-(-)-pindolol ((2*S*)-1-(1*H*-indol-4-yloxy)-3-(isopropylamino)-2-propanol);
- carpindolol (4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1*H*-indole-2-carboxylic acid 1-methylethyl ester); and
- 5 - pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- SB-224289 ((1'-methyl-6,7-dihydro-5*H*-spiro[furo[2,3-*f*]indole-3,4'-piperidin]-5-yl)[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]methanone);
- 10 - SB-216641 (*N*-{3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl}-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
- AR-A000002 ((*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide);
- GR-55562 (3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide);
- 15 - NAS-181 ((2*R*)-2-({[3-(4-morpholinylmethyl)-2*H*-chromen-8-yl]oxy}methyl)morpholine methanesulfonate (1:2));
- GR-127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);
- 20 - LY-393558 (1-{2-[4-(6-fluoro-1*H*-indol-3-yl)-3,6-dihydro-1(2*H*)-pyridinyl]ethyl}-3-isopropyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide); and
- pharmaceutically acceptable salts or esters thereof.

In one embodiment, the 5-HTR<sub>1B</sub> inhibitor according to the present invention is selected from the group comprising or consisting of:

- SB-224289 ((1'-methyl-6,7-dihydro-5*H*-spiro[furo[2,3-*f*]indole-3,4'-piperidin]-5-yl)[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]methanone);
- SB-216641 (*N*-{3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl}-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenylcarboxamide);

- AR-A000002 ((*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide); and
- pharmaceutically acceptable salts or esters thereof.

In a second embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is an antibody that blocks 5-HTR1<sub>B</sub> activation (*i.e.*, a 5-HTR1<sub>B</sub> blocking antibody). The 5-HTR1<sub>B</sub> blocking antibodies contemplated in the present invention may, for instance, impair the binding of 5-HT to the receptor by binding to said receptor.

In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is a polyclonal antibody, preferably a 5-HTR1<sub>B</sub> polyclonal blocking antibody.

10 In a preferred embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is a monoclonal antibody, preferably a 5-HTR1<sub>B</sub> monoclonal blocking antibody.

In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is a humanized antibody, preferably a 5-HTR1<sub>B</sub> humanized blocking antibody.

15 In a third embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is an aptamer that can block 5-HTR1<sub>B</sub> activation.

In a fourth embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is a polynucleotide.

In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is a polynucleotide which interferes with 5-HTR1<sub>B</sub> synthesis. In one embodiment, the synthesis of 5-HTR1<sub>B</sub> may be block at the transcriptional level. In one embodiment, the synthesis of 5-HTR1<sub>B</sub> may be block at the translational level.

20

In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is an antisense oligonucleotide. Antisense oligonucleotides, including antisense RNA molecules and antisense DNA molecules, would act to directly block the translation of 5-HTR1<sub>B</sub> mRNA by binding thereto and thus preventing protein translation or increasing mRNA degradation, thus decreasing the level of 5-HTR1<sub>B</sub>, and subsequently, 5-HTR1<sub>B</sub> activity, in a cell. For example, antisense oligonucleotides of at least about 15 bases and

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complementary to unique regions of the mRNA transcript sequence encoding 5-HTR1<sub>B</sub> can be synthesized, *e.g.*, by conventional phosphodiester techniques and administered by, *e.g.*, intravenous injection or infusion.

In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is a  
5 ribozyme.

In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is an interference RNA (RNAi). The term RNAi, as used herein, include, without limitation, small interfering RNAs (siRNAs), small hairpin RNAs (shRNAs) and microRNAs (miRNAs), targeted to a 5-HTR1<sub>B</sub> transcript; as well as RNAi vectors whose presence  
10 within a cell results in the production of an siRNA, shRNA or miRNA targeted to the target 5-HTR1<sub>B</sub> transcript. Such siRNA, shRNA or miRNA comprises a portion of RNA that is complementary to a region of the target 5-HTR1<sub>B</sub> transcript. Essentially, the RNAi contemplated in the present invention downregulates expression of 5-HTR1<sub>B</sub> via RNA interference.

15 In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is an siRNA.

Exemplary siRNA inhibiting 5-HTR1<sub>B</sub> include, but are not limited to, the siRNA purchased from Dharmacon used in the example section.

In one embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention is  
20 polynucleotide for targeted gene editing.

In one embodiment, any of the polynucleotide according to the present invention may be delivered *in vivo* alone or in association with a vector.

In a fifth embodiment, the 5-HTR1<sub>B</sub> inhibitor according to the present invention can be further identified by screening methods described in the state of the art and already  
25 mentioned hereinabove.

The present invention further relates to a combination of a 5-HTR1<sub>D</sub> inhibitor and at least one inhibitor of 5-hydroxytryptamine receptor 1B (5-HTR1<sub>B</sub>) for use in the prevention



and/or treatment of cancer in a subject in need thereof wherein said 5-HTR<sub>1D</sub> inhibitor and/or 5-HTR<sub>1B</sub> is preferably selected from the group comprising small organic molecules, antibodies, aptamers and polynucleotides.

The present invention further relates to a composition comprising a 5-HTR<sub>1D</sub> inhibitor  
5 according to the present invention, for use in the prevention and/or treatment of cancer.

In another embodiment, the present invention relates to a composition comprising a 5-HTR<sub>1D</sub> inhibitor and at least one inhibitor of 5-hydroxytryptamine receptor 1B (5-HTR<sub>1B</sub>) according to the present invention, for use in the prevention and/or treatment of cancer.

10 The present invention further relates to a pharmaceutical composition comprising a 5-HTR<sub>1D</sub> inhibitor according to the present invention, and at least one pharmaceutically acceptable excipient, for use in the prevention and/or treatment of cancer.

The present invention further relates to a pharmaceutical composition comprising a 5-HTR<sub>1D</sub> inhibitor, at least one inhibitor of 5-hydroxytryptamine receptor 1B (5-HTR<sub>1B</sub>)  
15 according to the present invention, and at least one pharmaceutically acceptable excipient, for use in the prevention and/or treatment of cancer.

In one embodiment, the pharmaceutical composition comprises the 5-HTR<sub>1D</sub> inhibitor according to the present invention in a therapeutically effective amount.

In one embodiment, the pharmaceutical composition comprises the 5-HTR<sub>1D</sub> inhibitor,  
20 at least one 5-HTR<sub>1B</sub> according to the present invention in a therapeutically effective amount.

As used herein, a “**pharmaceutically acceptable excipient**” refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Pharmaceutically acceptable excipients that may be used in the compositions  
25 according to the present invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine

sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, silica, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances (*e.g.*, sodium carboxymethylcellulose), polyethylene glycol, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical composition according to the present invention may further comprise antioxidant agents, including, but not limited to, ascorbic acid, ascorbyl palmitate, BHT, potassium sorbate or *Rosmarinus officinalis* extracts.

The pharmaceutical composition according to the present invention may further comprise flavour agents, including, but not limited to, sugars, fruit or tea flavourings.

The pharmaceutical composition according to the present invention may further comprise pharmaceutically acceptable salts, including, but not limited to, acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The excipient can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils such as oleic acid. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin (*i.e.*, soy lecithin or de-greased soy lecithin), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

For a prolonged absorption of the pharmaceutical composition according to the present invention, agents delaying absorption can be added, including, but not limited to,  
5 aluminium monostearate and gelatine.

The present invention further relates to a medicament comprising a 5-HTR<sub>1D</sub> inhibitor according to the present invention, for use in the prevention and/or treatment of cancer.

In one embodiment, present invention further relates to a medicament comprising the 5-HTR<sub>1D</sub> inhibitor, at least one 5-HTR<sub>1B</sub> according to the present invention in a  
10 therapeutically effective amount.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: gynecological cancer, liver cancer, lung cancer, gastrointestinal cancer,  
15 nervous system cancer, mesotheliomas, head and neck cancer, genitourinary tract cancer, sarcoma, cardiac cancer, bone cancer, hematologic and lymphoid cancer, skin cancer, thyroid gland cancer and adrenal glands cancer.

Examples of gynecological cancers include, but are not limited to, breast cancer, cervical cancer, ovarian cancer, uterine cancer, vulvar cancer and vaginal cancer.

20 Examples of breast cancers include, but are not limited to, triple negative breast cancer; luminal A breast cancer; luminal B breast cancer; and HER-2-enriched breast cancer.

Examples of ovarian cancers include, but are not limited to, dysgerminoma; granulosa-theca cell tumors; Sertoli-Leydig cell tumors;

Examples of uterine cancers include, but are not limited to, endometrial cancer such as  
25 endometrial carcinomas, endometrial stromal sarcomas and malignant mixed Müllerian tumors; uterine sarcomas; leiomyosarcomas; and gestational trophoblastic disease.

Examples of vulvar cancers include, but are not limited to, squamous cell vulvar carcinoma; verrucous vulvar carcinoma; vulvar melanoma; basal cell vulvar carcinoma; Bartholin gland carcinoma; vulvar adenocarcinoma; and erythroplasia of Queyrat.

5 Examples of vaginal cancers include, but are not limited to, squamous-cell vaginal carcinoma; vaginal adenocarcinoma; clear cell vaginal adenocarcinoma; vaginal germ cell tumors; vaginal sarcoma botryoides; and vaginal melanoma.

Examples of liver cancers include, but are not limited to, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma and hemangioma.

10 Examples of lung cancers include, but are not limited to, adenocarcinoma, bronchogenic carcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, lung sarcoma, lymphoma, chondromatous hamartoma and pleural mesothelioma.

15 Examples of gastrointestinal cancers include, but are not limited to, pancreatic cancer (such as, *e.g.*, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors or vipoma), esophageal cancer (such as, *e.g.*, squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma or lymphoma), stomach or gastric cancer (such as, *e.g.*, carcinoma, lymphoma or leiomyosarcoma), small bowel or small intestines cancer (such as, *e.g.*, adenocarcinoma lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma or fibroma), large bowel or large  
20 intestines cancer (such as, *e.g.*, adenocarcinoma, tubular adenoma, villous adenoma, hamartoma or leiomyoma) and colorectal cancer.

Examples of mesotheliomas include, but are not limited to, pleural mesothelioma, peritoneal mesothelioma, pericardial mesothelioma and end stage mesothelioma.

25 Examples of nervous system cancers include, but are not limited to, brain cancer (such as, *e.g.*, astrocytoma, medulloblastoma, glioma, lower grade glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, glioma or sarcoma), skull

cancer (such as, *e.g.*, osteoma, hemangioma, granuloma, xanthoma or osteitis deformans) and meninges cancer (such as, *e.g.*, meningioma, meningiosarcoma or gliomatosis).

Examples of head and neck cancers include, but are not limited to, head and neck squamous cell carcinoma and oral cancer (such as, *e.g.*, buccal cavity cancer, lip cancer, tongue cancer, mouth cancer or pharynx cancer).

Examples of genitourinary tract cancers include, but are not limited to, kidney cancer (such as, *e.g.*, clear renal cell carcinoma, chromophobe renal cell carcinoma, papillary renal cell carcinoma, adenocarcinoma, Wilm's tumor, nephroblastoma, lymphoma or leukemia), bladder and urethra cancer (such as, *e.g.*, squamous cell carcinoma, transitional cell carcinoma or adenocarcinoma), prostate cancer (such as, *e.g.*, adenocarcinoma or sarcoma) and testis cancer (such as, *e.g.*, seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors or lipoma).

Examples of sarcomas include, but are not limited to, Askin's tumor; sarcoma botryoides; chondrosarcoma; Ewing's sarcoma; malignant hemangioendothelioma; malignant schwannoma; osteosarcoma; and soft tissue sarcomas.

Examples of soft tissue sarcomas include, but are not limited to, alveolar soft part sarcoma; angiosarcoma; cystosarcoma phyllodes; dermatofibrosarcoma protuberans; desmoid tumor; desmoplastic small round cell tumor; epithelioid sarcoma; extraskeletal chondrosarcoma; extraskeletal osteosarcoma; fibrosarcoma; gastrointestinal stromal tumor (GIST); hemangiopericytoma; hemangiosarcoma; Kaposi's sarcoma; leiomyosarcoma; liposarcoma; lymphangiosarcoma; lymphosarcoma; malignant peripheral nerve sheath tumor (MPNST); neurofibrosarcoma; plexiform fibrohistiocytic tumor; rhabdomyosarcoma; synovial sarcoma; and undifferentiated pleomorphic sarcoma.

Examples of cardiac cancers include, but are not limited to, sarcoma (such as, *e.g.*, angiosarcoma, fibrosarcoma, rhabdomyosarcoma or liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma.

Examples of bone cancers include, but are not limited to, osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocyoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma and reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma, osteocartilaginous exostoses, benign chondroma, chondroblastoma, chondromyxoflbroma, osteoid osteoma and giant cell tumors.

Examples of hematologic and lymphoid cancers include, but are not limited to, blood cancer (such as, *e.g.*, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma or myelodysplasia syndrome), Hodgkin's disease, non-Hodgkin's lymphoma and hairy cell and lymphoid disorders.

Examples of skin cancers include, but are not limited to, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles, dysplastic nevi, lipoma, angioma and dermatofibroma.

Examples of thyroid gland cancers include, but are not limited to, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, undifferentiated thyroid cancer, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma and paraganglioma.

Examples of adrenal glands cancers include, but are not limited to, neuroblastoma and pheochromocytoma.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: breast cancer, cervical cancer, ovarian cancer, uterine cancer, vulvar cancer, vaginal cancer, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, bronchogenic carcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, lung sarcoma, lung lymphoma, lung chondromatous hamartoma, lung mesothelioma, pancreatic cancer, esophageal cancer, stomach (or gastric) cancer, small bowel or small

intestines cancer, large bowel or large intestines cancer, colorectal cancer, brain cancer, skull cancer, meninges cancer, head and neck squamous cell carcinoma, oral cancer, kidney cancer, bladder and urethra cancer, prostate cancer, testis cancer, cardiac sarcoma, cardiac myxoma, cardiac rhabdomyoma, cardiac fibroma, cardiac lipoma and cardiac  
5 teratoma, osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma and reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochondroma, osteochondrogenous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, blood cancer, Hodgkin's  
10 disease, non-Hodgkin's lymphoma, hairy cell and lymphoid disorders, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, keratoacanthoma, moles, dysplastic nevi, lipoma, angioma, dermatofibroma, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, undifferentiated thyroid cancer, multiple endocrine neoplasia type 2A, multiple endocrine  
15 neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma, neuroblastoma and pheochromocytoma.

In one embodiment, the 5-HT<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or  
20 consisting of: breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer (including, but not limited to, lung adenocarcinoma), pancreas cancer, brain cancer (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck  
25 cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including, but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and papillary renal cell carcinoma), gastric cancer, cervical cancer (including, but not limited to, cervical squamous cell carcinoma), ovarian cancer and sarcoma.

In one embodiment, the 5-HT<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for  
30

use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), lung cancer (including, but not limited to, lung adenocarcinoma), pancreas cancer, brain cancer  
5 (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including, but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and papillary renal cell carcinoma), gastric cancer, cervical cancer (including, but not limited to, cervical squamous cell carcinoma), ovarian cancer and sarcoma.

10 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: breast cancer (including, but not limited to, triple negative breast cancer, HER-2 enriched breast cancer, luminal A breast cancer and luminal B breast cancer),  
15 liver cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer (including, but not limited to, lung adenocarcinoma), brain cancer (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including, but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and  
20 papillary renal cell carcinoma), gastric cancer and cervical cancer (including, but not limited to, cervical squamous cell carcinoma).

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or  
25 consisting of: breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), lung cancer (including, but not limited to, lung adenocarcinoma), brain cancer (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including,  
30 but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and



papillary renal cell carcinoma), gastric cancer and cervical cancer (including, but not limited to, cervical squamous cell carcinoma).

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer (including, but not limited to, lung adenocarcinoma), brain cancer (including, but not limited to, brain lower grade glioma) and mesothelioma.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), lung cancer (including, but not limited to, lung adenocarcinoma), brain cancer (including, but not limited to, brain lower grade glioma) and mesothelioma.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: breast cancer (including, but not limited to, triple negative breast cancer, HER-2 enriched breast cancer, luminal A breast cancer and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma) and lung cancer (including, but not limited to, lung adenocarcinoma).

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: breast cancer (including, but not limited to, triple negative breast cancer,

HER2-enriched, luminal A breast cancer and luminal B breast cancer) and lung cancer (including, but not limited to, lung adenocarcinoma).

5 In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer in a subject, wherein said cancer is selected from the group comprising or consisting of breast cancer (including but not limited to triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer) and mesothelioma.

10 In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: triple negative breast cancer, luminal A breast cancer, luminal B breast cancer, liver cancer (including, but not limited to, liver hepatocellular carcinoma), mesothelioma and sarcoma.

15 In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer selected from the group comprising or consisting of: triple negative breast cancer, luminal A breast cancer, luminal B breast cancer, mesothelioma and sarcoma.

20 In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer in a subject, wherein high expression of 5-HTR1<sub>D</sub> or the high expression of 5-HTR1<sub>D</sub> and of 5-HTR1<sub>B</sub> in said cancer is associated with a lower survival of said subject.

25 In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer in a subject, wherein high expression of 5-HTR1<sub>D</sub> in said cancer is associated with a lower survival of said subject.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer in a subject, wherein high expression of 5-HTR1<sub>B</sub> in said cancer is associated with a lower survival of said subject.

- 5 In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer in a subject, wherein high expression of 5-HTR1<sub>D</sub> and of 5-HTR1<sub>B</sub> in said cancer is associated with a lower survival of said subject.
- 10 In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of cancer in a subject, wherein high expression of 5-HTR1<sub>D</sub> and low expression of 5-HTR1<sub>B</sub> in said cancer is associated with a lower survival of said subject.
- 15 Association between the level of expression of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>, and life expectancy of a subject can be determined using methods well-known in the art, such as the method described hereinafter.

- In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for
- 20 use in the prevention and/or treatment of cancer in a subject, wherein cells of said cancer overexpress the gene coding for 5-HTR1<sub>D</sub> or overexpress the gene coding for 5-HTR1<sub>D</sub> and overexpress the gene coding for 5-HTR1<sub>B</sub>.

- In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for
- 25 use in the prevention and/or treatment of cancer in a subject, wherein cells of said cancer overexpress the gene coding for 5-HTR1<sub>D</sub>.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for

use in the prevention and/or treatment of cancer in a subject, wherein cells of said cancer overexpress the gene coding for 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub>.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for  
5 use in the prevention and/or treatment of cancer in a subject, wherein cells of said cancer overexpress the gene coding for 5-HTR1<sub>D</sub> but do not overexpress the gene coding for 5-HTR1<sub>B</sub>.

The Inventors have demonstrated that a high level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> expression is particularly associated with a lower survival of breast cancer patients.  
10 These observations suggest that the inhibition of the activity of these receptors is particularly effective in the treatment of breast cancer.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of breast cancer in a subject.

15 Routinely evaluated markers of breast cancer cells, such as the presence or absence of the hormone receptors (HR) for estrogen and progesterone, the level of human epidermal growth factor receptor 2 (HER2), and the cell proliferation markers Ki67, are used to classify breast cancer into 4 molecular subtypes:

- HER2-enriched breast cancer (HR<sup>-</sup>/HER2<sup>+</sup>),
- 20 - luminal A breast cancer (HR<sup>+</sup>/HER2<sup>-</sup>),
- luminal B breast cancer (HR<sup>+</sup>/HER2<sup>+</sup>/Ki67<sup>+</sup>), and
- triple negative breast cancer (HR<sup>-</sup>/HER2<sup>-</sup>).

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for  
25 use in the prevention and/or treatment of triple negative, HER2-enriched, luminal A breast cancer or luminal B breast cancer in a subject.

Notably, the Inventors have demonstrated that a high level of 5-HTR1<sub>D</sub> or 5-HTR1<sub>B</sub> expression is particularly associated with a lower survival of triple negative breast cancer

patient. Moreover, the inhibition of 5-HTR<sub>1D</sub> and/or 5-HTR<sub>1B</sub> is particularly efficient in inhibiting proliferation and survival of triple negative breast cancer cell lines. The Inventors have also demonstrated that a high level of 5-HTR<sub>1D</sub> expression is particularly associated with a lower survival of luminal A breast cancer patient. These  
5 observations suggest that inhibiting the activity of these receptors is particularly effective for the treatment of triple negative breast cancer, luminal A breast cancer patients, and/or luminal B breast cancer.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for  
10 use in the prevention and/or treatment of triple negative, HER2-enriched, luminal A or luminal B breast cancer in a subject.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of triple negative breast cancer in a subject.

15 Triple negative breast cancers have been classified into different subtype by Lehmann *et al.*, J Clin Invest. 2011 Jul;121(7):2750-67.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of triple negative breast cancer in a subject wherein  
20 said triple negative breast cancer is of the type TNBC-BL1, TNBC-M and TNBC-UNS.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the prevention and/or treatment of luminal A breast cancer in a subject.

The Inventors have demonstrated that a level of 5-HTR<sub>1D</sub> receptor or 5-HTR<sub>1B</sub> receptor  
25 expression is particularly high in tumor samples not responding to chemotherapy.

Examples of chemotherapies include, but are not limited to:

- a. alkylating agents that act mainly by forming covalent bonds between DNA bases, including, but not limited to, nitrogen mustards (*e.g.*, cyclophosphamide),

- aziridines and epoxides (*e.g.*, thiopeta), alkyl sulfonates (*e.g.*, busulfan), nitrosureas (*e.g.*, BCNU and CCNU), hydrazine and triazine derivatives (*e.g.*, procarbazine and temozolomide);
- 5 b. cisplatin and its analogs that act by forming DNA adducts which lead to intra-strand and inter-strand linking leading to the formation of DNA filaments, including, but not limited to, carboplatin, cisplatin and oxaliplatin;
- c. antimetabolites including but not limited to folate metabolism inhibitors (*e.g.*, methotrexate, trimetrexate, tomudex), 5-fluoropyrimidines (*e.g.*, 5-FU), oral fluoropyrimidines (*e.g.*, tegafur, uracil, capecitabine), nucleoside analogs  
10 (*e.g.*, cytarabine), gemcitabine and 6-thiopurines (*e.g.*, 6-MP and 6-TG);
- d. topoisomerase-interactive agents that affect the topologic states of DNA by interfering or modulating DNA cleavage, strand passage and re-ligation, including, but not limited to, epipodophyllotoxins (*e.g.*, etoposide and teniposide), camptothecin analogs, anthracyclines (*e.g.*, doxorubicin, daunorubicin, epirubicin, idarubicin), mitoxantrone and losoxantrone, and dactinomycin;  
15 e. antimicrotubule agents, which interfere with the proper polymerization/depolymerization of microtubules, including, but not limited to, vinca alkaloids (*e.g.*, vincristine, vinorelbine and vinblastine), taxanes (*e.g.*, paclitaxel, docetaxel) and estramustine phosphate; and
- 20 f. numerous miscellaneous agents exist which cannot be classified into any of the above groups, including but not limited to suramin, bleomycin, L-asparaginase and amifostine.

In one embodiment, the 5-HTR1D inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the  
25 prevention and/or treatment of breast cancer (preferably, of triple negative or luminal A breast cancer) unresponsive to chemotherapy in a subject.

In one embodiment, said breast cancer (preferably, triple negative or luminal A breast cancer) is unresponsive to a first-line chemotherapy. “**First-line chemotherapy**”, as used herein, refers to an initial chemotherapy treatment given to a subject for the treatment of  
30 cancer.

In one embodiment, said breast cancer (preferably, triple negative or luminal A breast cancer) is unresponsive to a second-line chemotherapy. “**Second-line chemotherapy**”, as used herein, refers a chemotherapy treatment given when the first-line chemotherapy treatment did not work or stopped working.

- 5 In one embodiment, said breast cancer (preferably, triple negative or luminal A breast cancer) is unresponsive to a third-line chemotherapy or more. “**Third-line chemotherapy**”, as used herein, refers a chemotherapy treatment given when both the first-line chemotherapy treatment and the second-line chemotherapy treatment did not work or stopped working.
- 10 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered systemically or locally.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to  
15 be administered orally, buccally, by injection, by percutaneous administration, parenterally, intraperitoneal, by endoscopy, topically, transdermally, transmucosally, nasally, by inhalation spray, rectally, vaginally, intratracheally, or via an implanted reservoir.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the  
20 pharmaceutical composition or the medicament according to the present invention is to be orally administered.

Examples of formulations adapted to oral administration include, but are not limited to, solid forms, liquid forms and gels.

Examples of solid forms adapted to oral administration include, but are not limited to,  
25 pill, tablet, capsule, soft gelatin capsule, hard gelatin capsule, dragees, granules, caplet, compressed tablet, cachet, wafer, sugar-coated pill, sugar coated tablet, or dispersing/or disintegrating tablet, powder, solid forms suitable for solution in, or suspension in, liquid prior to oral administration and effervescent tablet.

Examples of liquid form adapted to oral administration include, but are not limited to, solutions, suspensions, drinkable solutions, elixirs, sealed phial, potion, drench, syrup, liquor and sprays.

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to  
5 be injected, preferably systemically injected.

Examples of formulations adapted to systemic injections include, but are not limited to, liquid solutions or suspensions, solid forms suitable for solution in, or suspension in, liquid prior to injection.

10 Examples of systemic injections include, but are not limited to, intravenous, intratumoral, intracranial, intralymphatic, intraperitoneal, intramuscular, subcutaneous, intradermal, intraarticular, intrasynovial, intrasternal, intrathecal, intravesical, intrahepatic, intralesional, intracavernous, infusion techniques and perfusion.

In another embodiment, when injected, the 5-HTR1<sub>D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is  
15 sterile. Methods for obtaining a sterile composition, pharmaceutical composition, medicament or nutraceutical composition include, but are not limited to, GMP synthesis (GMP stands for “Good manufacturing practice”).

In one embodiment, the 5-HTR1<sub>D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to  
20 be topically administered.

Examples of formulations adapted to topical administration include, but are not limited to, lubricants, sticks, lipsticks, waxes, creams, lotions, ointments, balms, gels, glosses, sunscreen preparations, cosmetics, masks, leave-on washes or cleansers, depilatory  
25 preparations and/or the like.

Topical administration characterizes the delivery, administration or application of the 5-HTR1<sub>D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention directly to the site of interest for a localized effect



- (generally onto one or more exposed or outer surfaces thereof, such as the outermost layer of the epidermis, which is exposed and visually observable), *e.g.*, using hands, fingers or a wide variety of applicators (rollup, roll-on or other stick container, tube container, cotton ball, powder puff, Q-tip, pump, brush, mat, cloth and/or the like). The application may be made, *e.g.*, by laying, placing, rubbing, sweeping, pouring, spreading and/or massaging into, or onto, the skin, or by any other convenient or suitable method. Preferably, topical administration is effected without any significant absorption of components of the composition into the subject's blood stream (to avoid a systemic effect).
- 10 The 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, *e.g.*, benzyl alcohol 1% or 2% (w/w) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain
- 15 polyethylene glycol 400 (PEG 400). They can be mixed to form ointments with, *e.g.*, benzyl alcohol 2% (w/w) as preservative, white petrolatum, emulsifying wax and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, *e.g.*, gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical
- 20 application.

- In one embodiment, the combination, the composition, pharmaceutical composition or medicament according to the present invention may be used in conjunction with delivery systems that facilitate delivery of the agents to the central nervous system. For example, various blood brain barrier (BBB) permeability enhancers may be used to transiently and
- 25 reversibly increase the permeability of the blood brain barrier to a treatment agent. Such BBB permeability enhancers include, but are not limited to, leukotrienes, bradykinin agonists, histamine, tight junction disruptors (*e.g.*, zonulin, zot), hyperosmotic solutions (*e.g.*, mannitol), cytoskeletal contracting agents, and short chain alkylglycerols (*e.g.*, 1-O-pentylglycerol). Oral, sublingual, parenteral, implantation, nasal and
- 30 inhalational routes can provide delivery of the active agent to the central nervous system.

In some embodiments, the 5-HTR1D inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention may be administered to the central nervous system with minimal effects on the peripheral nervous system.

5 In one embodiment, the 5-HTR1D inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered in an immediate release form.

In one embodiment, the 5-HTR1D inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered in a mixed-release form.

10 In one embodiment, the 5-HTR1D inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered in an enterically-coated form.

15 In one embodiment, the 5-HTR1D inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered in a sustained-release form.

In one embodiment, the 5-HTR1D inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention comprises a delivery system that controls the release of the active ingredients.

20 In one embodiment, the 5-HTR1D inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered at a dose determined by the skilled artisan and personally adapted to each subject.

25 It will be understood that the total daily usage of the 5-HTR1D inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective amount for any particular subject will depend upon a variety of factors including the condition being treated and the severity of the condition; the specific composition employed, the age, body weight,

general health, sex and diet of the subject; the time of administration, route of administration, the duration of the treatment; drugs used in combination or coincidental with the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a therapeutic compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved; but, at the opposite, it can be equally useful to start with a loading dose, a manner to reach steady-state plasma concentration more quickly, and then to follow with a maintenance dose calculated to exactly compensate the effect of the elimination process.

In one embodiment, a therapeutically effective amount of the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered at least once a day, at least twice a day, at least three times a day.

In one embodiment, a therapeutically effective amount of the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered every two, three, four, five, six days.

In one embodiment, a therapeutically effective amount of the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered twice a week, every week, every two weeks, every three weeks, once a month.

In one embodiment, a therapeutically effective amount of the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered every month, every two months, every three months, every four months, every five months, every six months, once a year.

In one embodiment, a therapeutically effective amount of the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered for a period of time of about one day, two days, three days, four days, five days, six days, a week, two weeks, three weeks, a month, two months,

three months, six months, a year, or over longer periods such as, *e.g.*, for several years or for the rest of the life of the subject.

In one embodiment, a therapeutically effective amount of the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered until treatment or alleviation of cancer, preferably selected from the group comprising or consisting of breast cancer (including but not limited to triple negative breast cancer and luminal A breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer (including, but not limited to, lung adenocarcinoma), brain cancer (including but not limited to brain lower grade glioma), mesothelioma, head and neck squamous cell carcinoma, kidney cancer (including but not limited to clear renal cell carcinoma, chromophobe renal cell carcinoma, papillary renal cell carcinoma) and cervix cancer (including but not limited to cervical squamous cell carcinoma); more preferably breast cancer, even more preferably triple negative or luminal A breast cancer.

In one embodiment, a therapeutically effective amount of the 5-HTR<sub>1D</sub> inhibitor, the composition, the pharmaceutical composition or the medicament according to the present invention is to be administered until the tumor(s) size has decreased, preferably the decrease of the tumor in size is of at least 50%, more preferably of at least 60 %, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 98%, at least 99% or more, of the size of the tumor before administration of the treatment.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the treatment of cancer in combination with chemotherapy.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the treatment of cancer in combination with chemotherapy, wherein said cancer is metastasized.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the treatment of cancer in combination with chemotherapy, wherein said cancer is metastasized and wherein said chemotherapy comprises the administration of taxanes, preferably of paclitaxel.

In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the treatment of cancer in combination with chemotherapy, wherein said chemotherapy comprises the administration of taxanes, preferably of paclitaxel.

10 In one embodiment, the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the sensitization to chemotherapy in a subject in need thereof. In one embodiment said cancer is unresponsive to chemotherapy.

15 In one embodiment the 5-HTR<sub>1D</sub> inhibitor, the combination, the composition, the pharmaceutical composition or the medicament according to the present invention is for use in the treatment of cancer in combination with an immune checkpoint inhibitor.

As used herein, the term “immune checkpoint inhibitor” refers to any compound, small molecule, coding or antisense nucleic acids, protein, antibody and fragment or functional equivalent thereof, having, intrinsically or via the protein encoded by said coding nucleic acids, the ability to antagonize the inhibition of the immune response by an immune checkpoint. In one embodiment, immune checkpoint inhibitor antagonizes at least partially (*e.g.*, more than 50%) the activity of inhibitory immune checkpoints, in particular those mediated by any of the following: programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), programmed death ligand-2 (PD-L2), lymphocyte-activation gene 3 (LAG3), T-cell immunoglobulin and mucin-domain containing protein 3 (TIM-3), B- and T-lymphocyte attenuator (BTLA), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), T cell immunoreceptor with Ig and ITIM domains (TIGIT), carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1) and killer immunoglobulin-like receptors (KIR).

Examples of immune checkpoint inhibitors include, but are not limited to, antibodies such as pembrolizumab (a.k.a. MK-3475, MK03475, lambrolizumab, SCH-900475 or Keytruda), nivolumab (a.k.a. ONO-4538, BMS-936558, MDX1106, GTPL7335 or Opdivo), cemiplimab (a.k.a. REGN2810 or REGN-2810), tislelizumab  
5 (a.k.a. BGB-A317), spartalizumab (a.k.a. PDR001 or PDR-001), ABBV-181, JNJ-63723283, BI 754091, MAG012, TSR-042, AGEN2034, avelumab, atezolizumab, durvalumab, LY3300054, ipilimumab, tremelimumab and IPH4102.

In one embodiment, the immune checkpoint inhibitor gene has, or encodes, a protein having a PD-1/PD-L1 inhibitory activity.

- 10 In one embodiment, the immune checkpoint inhibitor gene encodes an antibody, a mimetics thereof or a fragment thereof having a PD-1/PD-L1 immune checkpoint inhibitory activity.

In one embodiment, the immune checkpoint inhibitor gene encodes an antibody, a mimetic thereof or a fragment thereof, that specifically binds to PD-1 or PD-L1.

- 15 Example of anti-PD1 antibodies include, but are not limited to, nivolumab, cemiplimab, tislelizumab, spartalizumab, ABBV-181, JNJ-63723283, BI 754091, MAG012, TSR-042, AGEN2034, pidilizumab, nivolumab, pembrolizumab and antibodies described in International patent applications WO2004004771, WO2004056875, WO2006121168, WO2008156712, WO2009014708, WO2009114335, WO2013043569  
20 and WO2014047350.

Example of anti-PD-L1 antibodies include, but are not limited to, LY3300054, atezolizumab, durvalumab and avelumab.

- One may further consider as an immune checkpoint inhibitor in the context of the present invention the VISTA protein, which was shown to negatively regulate T cells. VISTA,  
25 also designated PD-1H or PD-L3, resembles members of the PD-L1 family. For example, anti-VISTA antibodies are described in US patent application US20130177557.

Another group to be considered as an immune checkpoint inhibitor is represented by inhibitors of the CTLA-4 protein, and especially an antibody (or mimetic or fragment

thereof) that recognizes human CTLA-4. CTLA4, also known as CD152, is encoded by the CTLA4 gene. CTLA4 is a member of the immunoglobulin superfamily of receptors. It is expressed on the surface of helper T cells where it primarily regulates the amplitude of the early stages of T cell activation. Recent work has suggested that CTLA-4 may  
5 function *in vivo* by capturing and removing B7.1 and B7.2 from the membranes of antigen-presenting cells, thus making these unavailable for triggering T-cell proliferation through CD28. A number of anti-CTLA-4 antibodies are available in the art (see, *e.g.*, those described in US patent US8,491,895). Other anti-CTLA-4 antibodies that can be considered in the context of this invention are FDA-approved or under advanced  
10 clinical development. One may cite more particularly ipilimumab (see, *e.g.*, US patents US6,984,720 and US8,017,114), tremelimumab (see, *e.g.*, US patents US7,109,003 and US8,143,379) and single chain anti-CTLA4 antibodies (see, *e.g.*, International patent applications WO1997020574 and WO2007123737).

Another group to be considered as an immune checkpoint inhibitor is represented by  
15 inhibitors of the LAG3 receptor (see *e.g.* US patent US5,773,578).

Another group to be considered as an immune checkpoint inhibitor is represented by inhibitors of the KIR proteins (KIR2L3 and KIR3DL2). KIR proteins are expressed by NK cells and T cells and promote self-tolerance by dampening lymphocyte activation, cytotoxic activity and cytokine release. Exemplary molecule targeting KIR that can be  
20 considered in the context of the present invention is IPH4102 targeting KIR3DL2.

In one embodiment, the subject is an animal, preferably a mammal, more preferably a primate, even more preferably a human.

In one embodiment, the subject is a male. In one embodiment, the subject is a female.

In one embodiment, the subject is a child. In one embodiment, the subject is a teenager.

25 In one embodiment, the subject is an adult.

In one embodiment, the subject is over 20 years old. In one embodiment, the subject is over 30 years old. In one embodiment, the subject is over 40 years old. In one

embodiment, the subject is over 50 years old. In one embodiment, the subject is over 55 years old. In one embodiment, the subject is over 60 years old.

In one embodiment, the subject is/was diagnosed with cancer. In one embodiment, the subject is/was diagnosed with breast cancer. In one embodiment, the subject is/was  
5 diagnosed with triple negative breast cancer. In one embodiment, the subject is/was diagnosed with luminal A breast cancer. In one embodiment, the subject is/was diagnosed with breast cancer unresponsive to chemotherapy. In one embodiment, the subject is/was diagnosed with metastasized cancer.

In one embodiment, the subject is/was diagnosed with cancer, wherein said cancer is  
10 characterized by the overexpression of 5-HTR1D and/or overexpression of 5-HTR1B.

The Inventors have demonstrated that high expression of 5-HTR1D is associated with a lower survival of subjects affected with breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer (including, but not limited to, lung adenocarcinoma), pancreas  
15 cancer, brain cancer (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including, but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and papillary renal cell carcinoma),  
20 cervical cancer (including, but not limited to, cervical squamous cell carcinoma), ovarian cancer and sarcoma.

The present invention hence relates to cancer prognosis methods, comprising a step of measuring the expression level of 5-HTR1D in a sample from the subject.

As used herein, the term “**prognosis**” refers to the likelihood of a given outcome in the  
25 development of a disease. Exemplary outcomes include, but are not limited to, improvement or worsening of the symptoms, death, survival, expectation of quality of life, potential complications and associated health issues. In the context of cancer, the outcome may include survival, long-term survival (*i.e.*, survival for at least 3, preferably



at least 5, 8, 10 years or more), survival without recurrence, survival without metastasis and responsiveness to chemotherapy.

The Inventors have further demonstrated that high level of expression of 5-HTR1D are characteristic of certain cancers.

- 5 The present invention hence relates to cancer diagnostic methods, comprising a step of measuring the expression level of 5-HTR1D in a sample of a subject.

As used herein, the term “**diagnostic**” refers to a technique or method to facilitate the identification of the nature and/or cause(s) of a medical condition or disease.

- 10 The Inventors have further demonstrated that the level of expression of 5-HTR1D allows the stratification of breast cancers, in particular in terms of response to chemotherapy. Indeed, the Inventors have surprisingly been able to correlate the high level of expression of 5-HTR1D with tumor unresponsiveness to chemotherapy.

The present invention hence relates to cancer stratification methods, comprising a step of measuring the expression level of 5-HTR1D in a sample of a subject.

- 15 As used herein, the term “**cancer stratification**” refers to the identification of a group of subjects with shared biological characteristics. These *ad hoc* defined groups can then be used in the design of clinical trials or to choose an appropriate course for the management of the cancer.

- 20 The measure of the expression level of 5-HTR1D in a sample of a subject is therefore indicative of stratification, diagnostic and prognosis, which can be combined accordingly in a single method.

The present invention hence relates to diagnostic and prognosis methods comprising a step of measuring the expression level of 5-HTR1D in a sample of a subject.

- 25 The present invention hence relates to diagnostic and stratification methods comprising a step of measuring the expression level of 5-HTR1D in a sample of a subject.

The present invention hence relates to stratification and prognosis methods comprising a step of measuring the expression level of 5-HTR1<sub>D</sub> in a sample of a subject.

The present invention hence relates to cancer diagnostic, stratification and prognosis methods comprising a step of measuring the expression level of 5-HTR1<sub>D</sub> in a sample of  
5 a subject.

The Inventors have further unveiled that high expression of 5-HTR1<sub>B</sub> may also be associated with a lower survival of patient with breast cancer (including, but not limited to, triple negative breast cancer and luminal A breast cancer) and mesothelioma. Furthermore, the Inventors have demonstrated that the expression level of 5-HTR1<sub>B</sub> is  
10 also useful in the context of stratification and diagnostic methods.

Together, the expression levels of both 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub> strengthen the effectiveness of the methods of diagnosis, prognosis and/or stratification according to the present invention.

The present invention hence relates to cancer diagnosis, stratification and/or prognosis  
15 methods comprising a step of measuring the expression level of 5-HTR1<sub>D</sub> in a sample.

In one embodiment, the cancer diagnosis, stratification and/or prognosis methods of the present invention comprise a step of measuring the expression levels of both 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub> in a sample.

In one embodiment, the invention relates to cancer diagnosis, stratification and/or  
20 prognosis methods, wherein said cancer is selected from the group comprising or consisting of breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer, and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma and cholangiocarcinoma), lung cancer (including, but not limited to, lung adenocarcinoma),  
25 pancreas cancer, brain cancer (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including, but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and papillary renal cell carcinoma),

cervical cancer, gastric cancer (including, but not limited to, cervical squamous cell carcinoma), ovarian cancer, sarcoma, thyroid cancer, colon cancer, bladder cancer and gastrointestinal cancer.

In one embodiment, the invention relates to cancer diagnosis, stratification and/or prognosis methods, wherein said cancer is selected from the group comprising or  
5 consisting of breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer, and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer (including, but not limited to, lung adenocarcinoma), pancreas cancer, brain cancer  
10 (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including, but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and papillary renal cell carcinoma), cervical cancer (including, but not limited to, cervical squamous cell carcinoma), ovarian cancer and sarcoma.

In one embodiment, the invention relates to cancer diagnosis, stratification and/or prognosis methods, wherein said cancer is selected from the group comprising or  
15 consisting of breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer  
20 (including, but not limited to, lung adenocarcinoma), pancreas cancer, brain cancer (including, but not limited to, brain lower grade glioma), mesothelioma, head and neck cancer (including, but not limited to, head and neck squamous cell carcinoma), kidney cancer (including, but not limited to, clear renal cell carcinoma, chromophobe renal cell carcinoma and papillary renal cell carcinoma) and cervical cancer (including, but not  
25 limited to, cervical squamous cell carcinoma).

In one embodiment, the invention relates to cancer diagnosis, stratification and/or prognosis methods, wherein said cancer is selected from the group comprising or  
consisting of breast cancer (including, but not limited to, triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer), liver  
30 cancer (including, but not limited to, liver hepatocellular carcinoma), lung cancer

(including, but not limited to, lung adenocarcinoma), brain cancer (including, but not limited to, brain lower grade glioma) and mesothelioma.

In one embodiment, the invention relates to cancer diagnosis, stratification and/or prognosis methods, wherein said cancer is selected from the group comprising or  
5 consisting of breast cancer (including, but not limited to, triple negative breast cancer, HER-2 enriched breast cancer, luminal A breast cancer and luminal B breast cancer), liver cancer (including, but not limited to, liver hepatocellular carcinoma) and lung cancer (including, but not limited to, lung adenocarcinoma).

In one embodiment, the invention relates to cancer diagnosis, stratification and/or  
10 prognosis methods, wherein said cancer is selected from the group comprising or consisting of breast cancer (including but not limited to triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer and luminal B breast cancer) and mesothelioma.

In one embodiment, the invention relates to cancer diagnosis, stratification and/or  
15 prognosis methods, wherein said cancer is selected from the group comprising or consisting of triple negative breast cancer, HER2-enriched breast cancer, luminal A breast cancer, luminal B breast cancer, liver cancer (including, but not limited to, liver hepatocellular carcinoma), mesothelioma and sarcoma.

In one embodiment, the cancer diagnosis, stratification and/or prognosis methods  
20 according to the invention comprise a step of measuring the expression level of 5-HTR1<sub>D</sub> or measuring the expression level of 5-HTR1<sub>D</sub> and of 5-HTR1<sub>B</sub> in a sample of the subject.

In one embodiment, the cancer diagnosis, stratification and/or prognosis methods according to the present the invention comprise a step of providing a sample from the subject.

25 In one embodiment, the sample is a body tissue sample. Examples of body tissues include, but are not limited to, breast, mesothelioma, liver, lung, brain, cervix, kidney, pancreas, ovary, skin, nerve, spleen, thymus, esophagus, stomach, intestine, testis, hair, skin, bone, uterus, bladder and spinal cord.

In one embodiment, the sample is a biopsy sample, preferably a cancer biopsy sample. In one embodiment, the sample is a fine-needle aspirate sample, preferably a cancer fine-needle aspirate sample. In one embodiment, the sample is a resection sample, preferably a cancer resection sample.

- 5 In one embodiment, the sample is a bodily fluid. Examples of bodily fluids include, but are not limited to, blood, plasma, serum, lymph, ascetic fluid, cystic fluid, urine, bile, nipple exudate, synovial fluid, bronchoalveolar lavage fluid, sputum, amniotic fluid, peritoneal fluid, cerebrospinal fluid, pleural fluid, pericardial fluid, semen, saliva, sweat and alveolar macrophages.
- 10 In one embodiment, the sample, preferably the cancer tissue sample, was previously taken from the subject, *i.e.*, the methods according to the present invention do not comprise a step of recovering a sample from the subject. Consequently, according to this embodiment, the methods according to the present invention are non-invasive methods, *i.e.*, *in vitro* methods.
- 15 In one embodiment, the step of measuring the expression level of 5-HTR1D and/or of 5-HTR1B can be carried out using methods well-known to the one skilled in the art.

In one embodiment, measuring the expression level comprises a sub-step of extracting total RNAs from the sample.

- 20 In one embodiment, measuring the expression level comprises a sub-step of retro-transcribing total RNAs extracted from the sample, thereby obtaining total cDNAs.

In one embodiment, measuring the expression level comprises a sub-step of amplifying, such as, *e.g.*, by PCR, preferably by qPCR, the cDNAs corresponding to 5-HTR1D and/or 5-HTR1B.

- 25 In one embodiment, the expression level of 5-HTR1D and/or 5-HTR1B is measured using a DNA microarray.

In one embodiment, the expression level of 5-HTR1D and/or 5-HTR1B is measured using RNAseq.

In one embodiment, the cancer diagnostic, stratification and/or prognosis methods according to the present invention comprise a step of comparing the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> determined in the sample of the subject, with a reference expression level.

- 5 The reference expression level may be either implemented in the software or an overall median or other arithmetic mean across measurements may be built.

In one embodiment, the reference expression level is relative to an expression level derived from population studies, including without limitation, such subjects having similar age range, subjects in the same or similar ethnic group, similar cancer history and  
10 the like.

In one embodiment, the reference expression level is derived from the measurement of the expression levels of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>, in a reference population.

In one embodiment, the reference population comprises subjects diagnosed with a given cancer, preferably at least 100, more preferably at least 250, even more preferably at least  
15 500 subjects diagnosed with said cancer.

In one embodiment, the reference population comprises subjects substantially healthy in respect to a given cancer, preferably at least 100, more preferably at least 250, even more preferably at least 500 subjects substantially healthy in respect to said cancer.

By implying a multitude of samples from the reference population, it is conceivable to  
20 calculate a median and/or mean expression level for 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>. In relation to these results, 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> expression value can be monitored as upregulated (or overexpressed), downregulated (or underexpressed) or substantially unchanged. In one embodiment, the reference expression level corresponds to the mean expression levels of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>, measured in the reference population.  
25 In one embodiment, the reference expression level corresponds to the median expression levels 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> measured in the reference population.

In one embodiment, 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is considered as differentially expressed (*i.e.*, overexpressed or underexpressed) in the sample from the subject as compared to the

reference expression level if expression levels differ (positively or negatively) by a factor of at least 1.1, preferably of at least 1.5, more preferably of at least 2 and even more preferably of at least 5.

5 In one embodiment, 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> expression level is considered as substantially unchanged in the sample from the subject as compared to the reference expression level if expression levels do not differ (positively or negatively) by a factor of more than 1.2, preferably 1.15, more preferably 1.1, even more preferably 1.05 or less.

10 In one embodiment, the cancer diagnostic, stratification and/or prognosis methods according to the present invention comprise a step of assigning the subject to a group based on the relation of the expression of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with their reference expression level.

15 It will be understood – and it is part of the knowledge of the one skilled in the art – that the assignment of a subject to a group or another, based on the relation between the measured level of expression of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with regard to their reference expression level, will depend on the reference expression level itself, *i.e.*, on the reference population used to determine the reference level of expression of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>.

20 In one embodiment, the subject may be assigned to a short survival group. As used herein, the term “**short survival group**” refers to a group of subjects having cancer and who are likely to die from said cancer within about 2, 3, 5, 8, 10 or more years.

In one embodiment, the subject is assigned to the short survival group if 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is substantially unchanged or overexpressed with respect to their reference expression level.

25 In one embodiment, the subject may be assigned to a long survival group. As used herein, the term “**long survival group**” refers to a group of subjects having cancer who are not likely to die from said cancer within about 2, 3, 5, 8, 10 or more years.

In one embodiment, the subject is assigned to the long survival group if 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is underexpressed or substantially unchanged with respect to the reference expression level.

5 In one embodiment, an outcome is considered as “not likely” if its probability is inferior to 0.5, preferably inferior to 0.4, 0.3, 0.2, 0.1 or less.

In one embodiment an outcome is considered as “likely” if its probability is superior to 0.5, preferably superior to 0.6, 0.7, 0.8, 0.9 or more.

In one embodiment, the subject may be assigned to a short metastasis-free survival group. As used herein, the term “**short metastasis-free survival group**” refers to a group of  
10 subjects having cancer and wherein said cancer is likely to metastasize within about 2, 3, 5, 8, 10 or more years.

In one embodiment, the subject is assigned to the short metastasis-free survival group if 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is substantially unchanged or overexpressed with respect to their reference expression level.

15 In one embodiment, the subject may be assigned to a long metastasis-free survival group. As used herein, the term “**long metastasis-free survival group**” refers to a group of subjects having cancer who are likely to survive without said cancer having metastasized for at least about 2, 3, 5, 8, 10 or more years.

20 In one embodiment, the subject is assigned to the long metastasis-free survival group if 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is underexpressed or substantially unchanged with respect to the reference expression level.

In one embodiment, the subject is assigned to a chemotherapy-resistant group. As used herein, the term “**chemotherapy-resistant group**” refers to a group of subjects having cancer and whose cancer is likely to be unresponsive to chemotherapy.

25 In one embodiment said subject has been previously treated with a chemotherapy.



In one embodiment, the subject is assigned to a chemotherapy-resistant group if 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is substantially unchanged or overexpressed with respect to their reference expression level.

5 In one embodiment, the subject is assigned to a chemotherapy-responsive group. As used herein, the term “**chemotherapy-responsive group**” refers to a group of subjects having cancer and whose cancer is likely to be responsive to chemotherapy. In one embodiment said subject has been previously treated with a chemotherapy.

10 In one embodiment, the subject is assigned to a chemotherapy-responsive group if 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is underexpressed or substantially unchanged with respect to their reference expression level.

In one embodiment, the subject is diagnosed with cancer.

In one embodiment, the subject is diagnosed with cancer if 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> is substantially unchanged or overexpressed with respect to their reference expression level.

15 In one embodiment, the cancer prognosis method according to the present invention comprises the steps of:

- a) measuring the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>, in a sample previously obtained from a subject,
- b) comparing the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with their reference expression level obtained from a reference population, and
- 20 c) assigning the subject to a survival group based on the comparison of the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with their reference expression level,

thereby prognosing survival in said subject.

25 In one embodiment, the cancer stratification method according to the present invention comprises the steps of:

- a) measuring the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>, in a sample previously obtained from a subject,

- b) comparing the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with their reference expression level obtained from a reference population, and
- c) assigning the subject to a chemotherapy response group based on the comparison of the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with their reference expression level,
- 5       thereby classifying said subject.

In one embodiment, the cancer diagnostic methods according to the present invention comprise the steps of:

- a) measuring the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub>, in a sample
- 10       previously obtained from a subject,
- b) comparing the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with their reference expression level obtained from a reference population, and
- c) diagnosing cancer in said subject on the basis of on the comparison of the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> with their reference expression
- 15       level.

The present invention further relates to a method for preventing and/or treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the composition, pharmaceutical composition or medicament according to the invention.

20

## BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1** is a graph showing the metastasis free survival (MFS) of breast cancer patients wherein said cancers have different level of expression of (A) 5-HTR1<sub>D</sub>, (B) 5-HTR1<sub>B</sub> or (C) both.

- 25       **Figure 2** is a graph showing the metastasis free survival (MFS) of luminal A breast cancer patients wherein said cancers have different level of expression of (A) 5-HTR1<sub>D</sub>, (B) 5-HTR1<sub>B</sub> or (C) both. HR: hormone receptor; ERBB2: Erb-B2 receptor tyrosine kinase 2 (HER2).

**Figure 3** is a graph showing the metastasis free survival (MFS) of triple negative breast cancer patients wherein said cancers have different level of expression of (A) 5-HTR1<sub>D</sub>, (B) 5-HTR1<sub>B</sub> or (C) both.

**Figure 4** is a graph showing the survival of pancreatic cancer patients wherein said  
5 cancers have different level of expression of 5-HTR1<sub>D</sub>.

**Figure 5** is a graph showing the survival of liver cancer patients wherein said cancers have different level of expression of 5-HTR1<sub>D</sub>. LIHC: liver hepatocellular carcinoma.

**Figure 6** is a graph showing the survival of lung cancer patients wherein said cancers have different level of expression of 5-HTR1<sub>D</sub>. LUAD: lung adenocarcinoma.

10 **Figure 7** is a graph showing the survival of brain cancer patients wherein said cancers have different level of expression of 5-HTR1<sub>D</sub>. LGG: lower grade glioma.

**Figure 8** is a graph showing the survival of mesothelioma patients wherein said cancers have different level of expression of (A) 5-HTR1<sub>B</sub> and (B) 5-HTR1<sub>D</sub>. MESO: mesothelioma.

15 **Figure 9** is a graph showing the survival of head and neck squamous cell carcinoma patients wherein said cancers have different level of expression of 5-HTR1<sub>D</sub>.

**Figure 10** is a graph showing the survival of kidney cancer patients wherein said cancers have different level of expression of 5-HTR1<sub>D</sub>. (A) KIRP: kidney renal papillary cell carcinoma; (B) KIRC: kidney renal clear cell carcinoma; (C) KICH: kidney chromophobe  
20 renal cell carcinoma.

**Figure 11** is a graph showing the survival of cervical squamous cell carcinoma (CESC) patients wherein said cancer have different level of expression of 5-HTR1<sub>D</sub>.

**Figure 12** is a graph showing the survival of gastric cancer patients wherein said cancers have different level of expression of 5-HTR1<sub>D</sub>.

25 **Figure 13** is a box plot showing the expression level of 5-HTR1<sub>D</sub> in normal and kidney renal papillary cell carcinoma tissues (KIRP). TCGA: the cancer genome atlas.

**Figure 14** is a box plot showing the expression level of 5-HTR1D in normal and lung adenocarcinoma tissues (LUAD). TCGA: the cancer genome atlas.

**Figure 15** is a box plot showing the expression level of 5-HTR1D in normal and pancreatic adenocarcinoma tissues (PAAD). TCGA: the cancer genome atlas.

- 5 **Figure 16** is a box plot showing the expression level of 5-HTR1D in normal and cervical squamous cell carcinoma tissues (CESC). TCGA: the cancer genome atlas.

**Figure 17** is a box plot showing the expression level of 5-HTR1D in normal and liver hepatocellular carcinoma tissues (LIHC). TCGA: the cancer genome atlas.

- 10 **Figure 18** is a box plot showing the expression level of 5-HTR1D in normal and head and neck squamous cell carcinoma tissues (HNSC). TCGA: the cancer genome atlas.

**Figure 19** is a box plot showing the expression level of 5-HTR1D in normal and rectum adenocarcinoma tissues (READ). TCGA: the cancer genome atlas.

**Figure 20** is a box plot showing the expression level of 5-HTR1D in normal and colon adenocarcinoma tissues (COAD). TCGA: the cancer genome atlas.

- 15 **Figure 21** is a box plot showing the expression level of 5-HTR1D in normal and Cholangiocarcinoma tissues (CHOL). TCGA: the cancer genome atlas.

**Figure 22** is a box plot showing the expression level of 5-HTR1D in normal and esophageal carcinoma tissues (ESCA). TCGA: the cancer genome atlas.

- 20 **Figure 23** is a box plot showing the expression level of 5-HTR1D in normal and thyroid carcinoma tissues (THCA). TCGA: the cancer genome atlas.

**Figure 24** is a box plot showing the expression level of 5-HTR1D in normal and uterine corpus endometrial carcinoma tissues (UCEC). TCGA: the cancer genome atlas.

**Figure 25** is a box plot showing the expression level of 5-HTR1D in normal and bladder urothelial carcinoma tissues (BLCA). TCGA: the cancer genome atlas.

**Figure 26** is a box plot showing the expression level of (A) 5-HTR1<sub>D</sub> and (B) 5-HTR1<sub>B</sub> in luminal breast cancer, HER2-enriched breast cancer, triple negative breast cancer and normal tissues.

**Figure 27** is a box plot showing the expression level of (A) 5-HTR1<sub>D</sub> and (B) 5-HTR1<sub>B</sub> in breast cancer tissues.

**Figure 28** is a box plot showing the expression level of (A) 5-HTR1<sub>D</sub> and (B) 5-HTR1<sub>B</sub> in tissues of Luminal, HER2-enriched and triple-negative breast cancer.

**Figure 29** is a box plot showing the expression level of (A) 5-HTR1<sub>D</sub> and (B) 5-HTR1<sub>B</sub> in tissues of different type of triple negative breast cancer as defined by Lehmann *et al.*, J Clin Invest. 2011 Jul;121(7):2750-67.

**Figure 30** shows histograms illustrating (A) the effect of BRL-15,572 treatment on the viability triple negative breast cancer cell lines; (B) the effect of BRL-15,572 treatment on apoptosis in the triple negative breast cancer cell line BT549; and (C) the effect of BRL-15,572 treatment on proliferation of the triple negative breast cancer cell line BT549. \* $p < 0.05$ , \*\*  $0.001 < p < 0.005$  and \*\*\* $p < 0.001$  Students t-test, in B and C.

**Figure 31** shows histograms illustrating (A) the effect of GR-127935 treatment on the viability triple negative breast cancer cell lines; (B) the effect of GR-127935 treatment on apoptosis in the triple negative breast cancer cell line BT549; and (C) the effect of GR-127935 treatment on the proliferation of the triple negative breast cancer cell line BT549. \* $p < 0.05$ , \*\*  $0.001 < p < 0.005$  and \*\*\* $p < 0.001$ , Student's t-test, in B and C.

**Figure 32** is a histogram illustrating the effect of *HTR1D* silencing on the viability of BT549 cells alone or with the combined silencing of *HTR1B*. (■  $p < 0.001$ ; Student's t-test).

## EXAMPLES

The present invention is further illustrated by the following examples.

### **Example 1: relation between expression of *HTR1D* and *HTR1B* and breast cancer patient's survival**

#### 5        Material and Methods

##### Patients

Primary breast tumor samples were obtained from 526 women treated at Institut Curie - Hôpital René Huguenin (Saint-Cloud, France) between 1978 and 2008. All patients treated at Institut Curie before 2007 were informed that their tumor samples might be  
10        used for scientific purposes and had the opportunity to decline. Since 2007, patients treated at Institut Curie have given their approval by signing an informed consent. This study was approved by the local ethics committee (Breast Group of Institut Curie - René Huguenin Hospital). The samples were immediately stored in liquid nitrogen until RNA extraction. A tumor sample was considered suitable for this study if the proportion  
15        of tumor cells exceeded 70%. All patients (mean age 60.9 years, range 29 – 91 years) met the following criteria: primary unilateral non-metastatic breast carcinoma for which complete clinicopathological data and follow-up were available; no radiotherapy or chemotherapy before surgery; and full follow-up at Institut Curie - Hôpital René Huguenin. Adjuvant therapy was administered to 367 patients, consisting of  
20        chemotherapy alone in 95, hormone therapy alone in 177, and both treatments in 95 patients. Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (ERBB2) statuses were determined at the protein level by biochemical methods (Dextran-coated charcoal method, enzyme immunoassay or immunohistochemistry) and confirmed by real-time quantitative RT-PCR.  
25        The population was divided into four groups according to hormone receptor (HR) (estrogen receptor - ER and progesterone receptor PR) and HER2/ERBB2 statuses as follows: two luminal subtypes [HR+ (ER $\alpha$ + or PR+)/ERBB2+ (n=58)] and [HR+ (ER $\alpha$ + or PR+)/ERBB2- (n=294)]; an ERBB2+ subtype [HR- (ER $\alpha$ - and PR-)/ERBB2+ (n=73)] and a triple-negative subtype [HR- (ER $\alpha$ - and PR-)/ERBB2- (n=101)]. Within a median

follow-up of 9.4 years (range 1 month to 33.2 years), 210 patients developed distant metastasis. Clinical characteristics of the cohort are described in **Table 1**.

**Table 1:** clinical characteristics of the cohort

|                                              | Number of patients (%) | Number with metastases (%) | p-value <sup>a</sup> |
|----------------------------------------------|------------------------|----------------------------|----------------------|
| <i>Total</i>                                 | 526 (100)              | 209 (39.7)                 |                      |
| <i>Age</i>                                   |                        |                            |                      |
| ≤50                                          | 125 (23.8)             | 52 (41.6)                  | 0.51 (NS)            |
| >50                                          | 401 (76.2)             | 157 (39.2)                 |                      |
| <i>SBR histological grade</i> <sup>b,c</sup> |                        |                            |                      |
| I                                            | 60 (11.7)              | 12 (20.0)                  | <b>0.0018</b>        |
| II                                           | 241 (47.2)             | 100 (41.5)                 |                      |
| III                                          | 210 (41.1)             | 93 (44.3)                  |                      |
| <i>Lymph node status</i> <sup>d</sup>        |                        |                            |                      |
| 0                                            | 160 (30.7)             | 48 (30.0)                  | <0.0001              |
| 1-3                                          | 248 (47.6)             | 87 (35.1)                  |                      |
| >3                                           | 113 (21.7)             | 72 (63.7)                  |                      |
| <i>Macroscopic tumor size</i> <sup>e</sup>   |                        |                            |                      |
| ≤25mm                                        | 248 (48.1)             | 76 (30.6)                  | <0.0001              |
| >25mm                                        | 268 (51.9)             | 132 (49.3)                 |                      |
| <i>ERα status</i>                            |                        |                            |                      |
| Negative                                     | 181 (34.4)             | 76 (42.0)                  | 0.096 (NS)           |
| Positive                                     | 345 (65.6)             | 133 (38.6)                 |                      |
| <i>PR status</i>                             |                        |                            |                      |
| Negative                                     | 254 (48.3)             | 109 (42.9)                 | <b>0.028</b>         |
| Positive                                     | 272 (51.7)             | 100 (36.8)                 |                      |
| <i>ERBB2 status</i>                          |                        |                            |                      |
| Negative                                     | 395 (75.1)             | 152 (38.5)                 | 0.19 (NS)            |
| Positive                                     | 131 (24.9)             | 57 (43.5)                  |                      |
| <i>Molecular subtypes</i>                    |                        |                            |                      |
| HR- ERBB2-                                   | 101 (19.2)             | 38 (37.6)                  | 0.072 (NS)           |
| HR- ERBB2+                                   | 73 (13.9)              | 36 (49.3)                  |                      |
| HR+ ERBB2-                                   | 294 (55.9)             | 114 (38.8)                 |                      |
| HR+ ERBB2+                                   | 58 (11.0)              | 21 (36.2)                  |                      |
| <i>PIK3CA mutation status</i> <sup>f</sup>   |                        |                            |                      |
| wild type                                    | 354 (68.1)             | 145 (41.0)                 | 0.21 (NS)            |
| mutated                                      | 166 (31.9)             | 61 (36.7)                  |                      |

- a Log-rank test. NS: not significant  
b Scarff Bloom Richardson classification  
c Information available for 511 patients  
d Information available for 521 patients  
e Information available for 516 patients  
f Information available for 520 patients

#### RNA extraction

Total RNA was extracted from breast tumor samples by using acid-phenol guanidium. RNA quality was determined by electrophoresis through agarose gels, staining with ethidium bromide, and visualization of the 18S and 28S RNA bands under ultraviolet light.

#### Real-time RT-PCR

Quantitative values were obtained from the cycle number (Ct value) at which the increase in the fluorescence signal associated with exponential growth of PCR products started to be detected by the laser detector of the ABI Prism 7900 Sequence Detection System (Perkin-Elmer Applied Biosystems, Foster City, CA), using PE Biosystems analysis software according to the manufacturer's manuals. The TBP gene (Genbank accession NM\_003194) encoding the TATA box-binding protein (a component of the DNA-binding protein complex TFIID) was quantified as an endogenous RNA control, and each sample was normalized on the basis of its TBP content. Results, expressed as N-fold differences in target gene expression relative to the TBP gene and termed "Ntarget", were determined as  $N_{\text{target}} = 2^{\Delta C_{\text{t sample}}}$ , where the  $\Delta C_{\text{t}}$  value of the sample was determined by subtracting the average Ct value of the target gene from the average Ct value of the TBP gene. The median target gene value of normal breast tissues (14 samples) was used as a reference to normalize the data. Primers' sequences are indicated below in **Table 2**. The conditions of cDNA synthesis and PCR have been described previously (Bièche *et al.*, Clin Chem. 1999; 45:1148–56).



**Table 2:** list of primers used in the RT-PCR experiments

| SEQ ID NO    | Name     | Sequence                |
|--------------|----------|-------------------------|
| SEQ ID NO: 1 | HTR1B-U2 | TGCAAAGATGCCTGCTGGTTC   |
| SEQ ID NO: 2 | HTR1B-L2 | TGGGGTTGATGAGGGAGTTGAG  |
| SEQ ID NO: 3 | HTR1D-U1 | CCACCTAGCATGTCCCCACTGA  |
| SEQ ID NO: 4 | HTR1D-L1 | TCCCAAGCCTCTGAGGTTTCTGT |
| SEQ ID NO: 5 | TBP-U    | TGCACAGGAGCCAAGAGTGAA   |
| SEQ ID NO: 6 | TBP-L    | CACATCACAGCTCCCCACCA    |

### Results

The metastasis-free survival (MFS) of breast cancer patients with a low level of *HTR1D* expression was longer than the MFS of breast cancer patients with a high level of *HTR1D* expression (**Fig. 1 A**). Similarly, the MFS of breast cancer patients with a low level of *HTR1B* expression was longer than the MFS of breast cancer patients with a high level of *HTR1B* expression (**Fig. 1 B**). Breast cancer patients expressing both genes at a low level showed a longer MFS than breast cancer patients expressing both genes at a high level (**Fig. 1C**).

Considering HR+ERBB2 breast cancer patients, similar results were obtained: **Fig. 2** is a graph showing the metastasis free survival (MFS) of luminal A breast cancer patients wherein said cancers have different level of expression of (**Fig. A**) 5-HTR1D, (**Fig. B**) 5-HTR1B or (**Fig. C**) both.).

In breast cancer patient of the triple negative (TN) group, MFS also negatively correlated with the expression level of the *HTR1D* gene (**Fig. 3 A**), *HTR1B* gene (**Fig. 3 B**) or *HTR1D* and *HTR1B* genes (**Fig. 3 C**).

### Conclusion

The MFS of breast cancer patients correlates negatively with the expression level of the *HTR1D* and/or *HTR1B* gene(s) in breast cancer patients, breast cancer patient of the luminal A group and breast cancer patient of the TN group.

These results suggest that the measure of the expression level of *HTR1D* and/or *HTR1B* gene(s) might be used in the diagnosis, prognosis and stratification of breast cancer patient. They also support the hypothesis that the inhibition of 5-HTR1D and / 5-HTR1B

could be useful in the treatment of breast cancer, in particular the triple negative and luminal A subtype.

## **Example 2: relation between expression of *HTR1D* and *HTR1B* and cancer patient's survival**

### **Material and Methods**

Kaplan-Meier curves illustrating the survival probability in different cancers based on transcriptomic levels of *HTR1D* or *HTR1B* were obtained using the current release of Ualcan web-tool. Transcriptomic data were also obtained using the current release of Ualcan web-tool, interrogating the database using *HTR1D* or *HTR1B* and selecting the different tumors types and molecular subtypes when indicated. (Chandrashekar *et al.*, Neoplasia. 2017 Aug;19(8):649-658). For gastric cancer, data were obtained using KM plot web-tool (www.kmplot.com) interrogating the database using probe ID "207368\_at".

### **Results**

Lower expression level of *HTR1D* was found associated with a longer survival of patients for several cancer type. Lower expression level of *HTR1B* was found associated with a longer survival of mesothelioma patients. The results of the analysis of cancer patient's survival are indicated in **Table 3** hereinafter.

**Table 3:** cancers wherein lower expression of *HTR1D* and/or *HTR1B* expression correlates with longer survival and corresponding analysis of *HTR1D* expression level.

| Cancer type                                    | survival <i>p</i> -value | Figure  |
|------------------------------------------------|--------------------------|---------|
| <i>HTR1B</i>                                   |                          |         |
| Mesothelioma (MESO)                            | 0.0032                   | Fig.8A  |
| <i>HTR1D</i>                                   |                          |         |
| Mesothelioma (MESO)                            | 0.0073                   | Fig 8B  |
| Lower Grade Glioma (LGG) – Brain               | 0.0018                   | Fig. 7  |
| gastric cancer                                 | 0.016                    | Fig .12 |
| Kidney Chromophobe Renal Cell Carcinoma (KICH) | 0.016                    | Fig.10C |

|                                              |         |                 |
|----------------------------------------------|---------|-----------------|
| Kidney Renal Clear Cell Carcinoma (KIRC)     | 0.014   | <b>Fig. 10B</b> |
| Kidney Renal Papillary Cell Carcinoma (KIRP) | 0.041   | <b>Fig. 10A</b> |
| Liver Hepatocellular Carcinoma (LIHC)        | 0.0034  | <b>Fig. 5</b>   |
| Lung Adenocarcinoma (LUAD)                   | 0.00041 | <b>Fig. 6</b>   |
| Head and Neck Squamous Cell Carcinoma (HNSC) | 0.013   | <b>Fig. 9</b>   |
| Pancreas                                     | 0.00053 | <b>Fig. 4</b>   |
| Cervical Squamous cell Carcinoma (CESC)      | 0.045   | <b>Fig. 11</b>  |

### Conclusion

These results suggest that the measure of the expression level of *HTR1D* and/or *HTR1B* gene(s) might be used in the diagnosis, prognosis and stratification of several cancer, in particular mesothelioma, glioma, gastric cancer, kidney cancer, liver cancer, lung cancer, head and neck squamous cell carcinoma, pancreas cancer and cervical cancer. Furthermore, in view of these results, the treatment of said cancer by the inhibition of 5-HTR<sub>1D</sub> and/or 5-HTR<sub>1B</sub> might be considered.

### **Example 3 *HTR1D* is overexpressed in several cancers**

#### 10 Material and Methods

Transcriptomic data were obtained using the current release of Ualcan web-tool, interrogating the database using *HTR1D* and selecting the different tumors types and molecular subtypes when indicated. (Chandrashekar *et al.*, Neoplasia. 2017 Aug;19(8): 649-658). For gastric cancer, data were obtained using KM plot web-tool  
15 (www.kmplot.com) interrogating the database using probe ID “207368\_at”.

### Results

Overexpression of *HTR1D* was found associated with several cancer type. The results of the analysis of cancer patient’s survival are indicated in **Table 4** hereinafter.

**Table 4:** cancers wherein overexpression of *HTR1D* is observed

| Cancer type                                  | Figure  |
|----------------------------------------------|---------|
| Kidney Renal Papillary Cell Carcinoma (KIRP) | Fig. 13 |
| Liver Hepatocellular Carcinoma (LIHC)        | Fig. 17 |
| Lung Adenocarcinoma (LUAD)                   | Fig. 14 |
| Head and Neck Squamous Cell Carcinoma (HNSC) | Fig. 18 |
| Pancreas                                     | Fig. 15 |
| Cervical Squamous cell Carcinoma (CESC)      | Fig. 16 |
| Rectum Adenocarcinoma (READ)                 | Fig. 19 |
| Colon Adenocarcinoma (COAD)                  | Fig. 20 |
| Cholangiocarcinoma (CHOL)                    | Fig. 21 |
| Esophageal Carcinoma (ESCA)                  | Fig. 22 |
| Thyroid carcinoma (THCA)                     | Fig. 23 |
| Uterine Corpus Endometrial Carcinoma (UCEC)  | Fig. 24 |
| Bladder Urothelial Carcinoma (BLCA)          | Fig. 25 |

### Conclusion

- 5 These results suggest that the measure of the expression level of *HTR1D* gene might be used in the diagnosis, prognosis and stratification of cancer, in particular kidney cancer, liver cancer, lung cancer, head and neck squamous cell carcinoma, pancreas cancer, cervical cancer, rectum cancer, colon cancer, cholangiocarcinoma, Esophageal cancer thyroid cancer, endometrial cancer and bladder cancer. They also support the hypothesis
- 10 that the inhibition of 5-HTR<sub>1D</sub> and / 5-HTR<sub>1B</sub> could be useful in the treatment of said cancer.

### **Example 4: 5-HT receptors expression in breast cancer**

#### Material and Methods

##### RNA extraction from breast cell lines

- 15 RNA was isolated from cell lines at 80% confluency with miRNeasy Mini kits (Qiagen, Courtaboeuf, France) following the manufacturer's instructions.

Affymetrix arrays

Microarray data (Affymetrix human exon 1.0 ST DNA array) of breast cell lines from Institut Curie comprising different breast cancer histological subtypes were queried for *HTR1D* and *HTR1B* transcripts. Boxplots illustrating each subtype and compared to non-tumorigenic breast cell lines were displayed.

Real-time reverse transcription-quantitative PCR

Reverse transcription was performed with 2 µg of total RNA, with the High-Capacity cDNA reverse transcription kit (Applied Biosystems). The seventeen 5-HT receptors (HTRs) and GAPDH were amplified by Q-PCR in a Roche LightCycler 480 real-time thermal cycler, with the Roche Taqman master mix (Roche) with couples of primers and probes designed with the Roche Assay Center tool (available online at [https://www.lifescience.roche.com/en\\_fr/brands/universal-probe-library.html#assay-design-center](https://www.lifescience.roche.com/en_fr/brands/universal-probe-library.html#assay-design-center)) or ready-to-use assay (encompassing primers and Taqman probes) purchased from Applied LifeTechnologies. Primers and probes sequences or reference are listed in **Table 5**.

**Table 5:** Primer used in the qPCR experiments

|       | SEQ ID NO     | Name                | Sequence                   |
|-------|---------------|---------------------|----------------------------|
| HTR1A | SEQ ID NO: 7  | HTR1A fwd           | ctcacggcttgacacct          |
|       | SEQ ID NO: 8  | HTR1A rev           | gctgggtctcctttgcac         |
|       | na            | Universal probe #4  | cttctctgc                  |
| HTR1B | SEQ ID NO: 9  | HTR1B fwd           | tgcatgaaactttatctgatagtcac |
|       | SEQ ID NO: 10 | HTR1B rev           | tgtagcacacaaggaatcac       |
|       | na            | Universal probe #12 | ctccttcc                   |
| HTR1D | SEQ ID NO: 11 | HTR1D fwd           | attctgggggcctttatcat       |
|       | SEQ ID NO: 12 | HTR1D rev           | agatggggaggaccagagac       |
|       | na            | Universal probe #71 | ctggctgc                   |
| HTR1E | SEQ ID NO: 13 | HTR1E fwd           | cgggttccgagtgcagactt       |
|       | SEQ ID NO: 14 | HTR1E rev           | agggccacagcatttcttc        |
|       | na            | Universal probe #36 | ggagccag                   |
| HTR1F | SEQ ID NO: 15 | HTR1F fwd           | aacaggaacatgaggagacga      |
|       | SEQ ID NO: 16 | HTR1F rev           | tgaatttaagaaatccattttcttgt |
|       | na            | Universal probe #9  | catcacca                   |
| HTR2A | SEQ ID NO: 17 | HTR2A fwd           | tgatgtcacttgccatagctg      |
|       | SEQ ID NO: 18 | HTR2A rev           | caggtaaaccagactgcacaa      |
|       | na            | Universal probe #3  | cccagcag                   |
| HTR2C | SEQ ID NO: 19 | HTR2C fwd           | ccgagtcggttctcgtcta        |

|       |                              |                     |                      |
|-------|------------------------------|---------------------|----------------------|
|       | SEQ ID NO: 20                | HTR2C rev           | tcgcggtgttagctgat    |
|       | na                           | Universal probe #27 | gctgcctg             |
| HTR3A | SEQ ID NO: 21                | HTR3A fwd           | gccaccaagactgatgactg |
|       | SEQ ID NO: 22                | HTR3A rev           | tcgggctcttcgaagtc    |
|       | na                           | Universal probe #5  | tgtggctg             |
| HTR3B | SEQ ID NO: 23                | HTR3B fwd           | agtgtaatggctcccctgtg |
|       | SEQ ID NO: 24                | HTR3B rev           | tcctggggatgatgttatct |
|       | na                           | Universal probe #83 | ggtggctg             |
| HTR4  | SEQ ID NO: 25                | HTR4 fwd            | gaacctgctggtgatggtg  |
|       | SEQ ID NO: 26                | HTR4 rev            | ccgcaaagcaagagataca  |
|       | na                           | Universal probe #27 | gctgcctg             |
| HTR5A | SEQ ID NO: 27                | HTR5A fwd           | gtctcaccatataccgaagc |
|       | SEQ ID NO: 28                | HTR5A rev           | ggacctggaacaccatctg  |
|       | na                           | Universal probe #53 | ctctgccca            |
| HTR6  | SEQ ID NO: 29                | HTR6 fwd            | agcaggaaggccctgaag   |
|       | SEQ ID NO: 30                | HTR6 rev            | gagatgcagtcgcacacg   |
|       | na                           | Universal probe #3  | cccagcag             |
| GAPDH | SEQ ID NO: 31                | GAPDH fwd           | agccacatcgctcagacac  |
|       | SEQ ID NO: 32                | GAPDH rev           | gcccaatacgaccaaatcc  |
|       | na                           | Universal probe #60 | tggggaag             |
| HTR2B | Taqman Assay # Hs00168362_m1 |                     |                      |
| HTR3C | Taqman Assay # Hs01118162_m1 |                     |                      |
| HTR3D | Taqman Assay # Hs00699392_g1 |                     |                      |
| HTR3E | Taqman Assay # Hs00704511_s1 |                     |                      |
| HTR7  | Taqman Assay # Hs0419478_s1  |                     |                      |

Transcriptomic expression levels for each HTR gene were calculated with the 2- $\Delta$ Ct method normalized to GAPDH as housekeeping gene and displayed as UAE (Arbitrary Unit of Expression).

#### Analysis of expression using Ualcan web-tool

- Transcriptomic data were obtained using the current release of Ualcan web-tool, interrogating the database using *HTR1D* or *HTR1B* and selecting the different tumors types and molecular subtypes when indicated. (Chandrashekar *et al.*, Neoplasia. 2017 Aug;19(8):649-658).

#### Results

- HTR1D* ((**Fig. 26 A**) was found overexpressed in triple negative breast cancer tissues from the patient cohort described in Example 1 while it was not the case for *HTR1B* (**Fig. 26 B**). Similarly, *HTR1D* (**Fig. 27 A**) was found overexpressed in breast cancer

tissues while it was not the case for *HTR1B* (**Fig. 27 B**) using the Cancer Genome Atlas (TCGA) transcriptome data. Using the same dataset, *HTR1D* was found overexpressed in tissues of Luminal, HER2- (**Fig. 28 A**) enriched and triple-negative breast cancers while it was not the case for *HTR1B* (**Fig. 28 B**). Detailed analysis revealed that *HTR1D* (**Fig. 29 A**) was overexpressed in the following type of triple-negative breast cancer (defined by Lehmann *et al.*, J Clin Invest. 2011 Jul;121(7):2750-67): TNBC-BL1, TNBC-M and TNBC-UNS while *HTR1B* was found underexpressed in the following type of triple negative breast cancer: TNBC-BL1, TNBC-LAR (**Fig. 29 B**). Furthermore, *HTR1D* was also found highly expressed in several triple negative cancer cell lines (**Table 6**).

**Table 6:** HTR receptor expression in cancer cell lines (Arbitrary Unit of Expression).

|              | <b>BT20</b> | <b>BT549</b> | <b>HCC38</b> | <b>HCC70</b> | <b>HCC1143</b> | <b>HCC1187</b> | <b>HCC1937</b> | <b>Hs578T</b> | <b>MDA MB 157</b> | <b>MDA MB 231</b> | <b>MDA MB 436</b> | <b>MDA MB 468</b> | <b>Cal51</b> |
|--------------|-------------|--------------|--------------|--------------|----------------|----------------|----------------|---------------|-------------------|-------------------|-------------------|-------------------|--------------|
| <b>HTR1A</b> | 6,2618E-06  | 3,1703E-05   | 2,5221E-05   | 1,7407E-05   | 1,6185E-05     | 3,6041E-05     | 6,4602E-06     | 9,2833E-05    | 6,7813E-06        | 6,972E-06         | 6,3492E-06        | 1,1766E-05        | 1,5365E-05   |
| <b>HTR1B</b> | 0,00042124  | 0,00054555   | 0,00011914   | 0,00032891   | 0,00017144     | 0,00019023     | 0,00048659     | 9,6775E-05    | 0,0002118         | 7,0354E-05        | 4,6417E-05        | 0,00010964        | 7,6192E-05   |
| <b>HTR1D</b> | 0,00135734  | 0,0094859    | 0,00213729   | 0,00459729   | 0,00699238     | 0,00019762     | 0,00172403     | 0,00111403    | 0,00060452        | 0,00191957        | 0,00072236        | 0,00096312        | 0,000606616  |
| <b>HTR1E</b> | NA          | NA           | NA           | NA           | NA             | 3,2301E-06     | NA             | NA            | NA                | NA                | 4,762E-06         | NA                | 5,924E-06    |
| <b>HTR1F</b> | NA          | 3,0664E-06   | 0,00012377   | NA           | NA             | 1,3723E-06     | NA             | 4,5839E-06    | 3,1594E-05        | NA                | NA                | NA                | NA           |
| <b>HTR2A</b> | NA          | 0,0105618    | 0,00340059   | 4,3971E-06   | NA             | NA             | NA             | 0,00056479    | 0,00020601        | NA                | NA                | 0,00002958        | NA           |
| <b>HTR2B</b> | NA          | 6,1411E-07   | 1,9841E-07   | NA           | NA             | NA             | 7,2372E-08     | 1,4226E-07    | 1,3885E-07        | 6,776E-08         | NA                | NA                | 2,2216E-06   |
| <b>HTR2C</b> | NA          | NA           | NA           | NA           | NA             | NA             | NA             | NA            | NA                | NA                | NA                | NA                | NA           |
| <b>HTR3A</b> | NA          | NA           | 3,1418E-06   | 0,00011194   | 2,5786E-06     | 1,1326E-05     | 3,4739E-06     | NA            | 4,5522E-06        | NA                | 5,7222E-06        | 2,8022E-06        | NA           |
| <b>HTR3B</b> | NA          | NA           | NA           | NA           | NA             | NA             | NA             | NA            | NA                | NA                | NA                | NA                | NA           |
| <b>HTR3C</b> | 2,5289E-07  | NA           | NA           | NA           | NA             | NA             | 1,9033E-07     | 9,0103E-06    | 1,9815E-06        | 3,4307E-07        | NA                | NA                | NA           |
| <b>HTR3D</b> | 4,5425E-07  | 3,9032E-05   | 7,7524E-05   | 9,8467E-05   | 0,00003073     | 0,00010336     | 1,9033E-07     | 0,00016276    | 3,344E-06         | 6,4826E-06        | 3,1788E-07        | 6,876E-06         | NA           |
| <b>HTR3E</b> | 2,6567E-05  | 7,7793E-05   | 0,00018761   | 0,00018375   | 0,00011549     | 0,00012903     | 0,00010019     | 0,00022779    | 3,9032E-05        | 1,7589E-05        | 1,5312E-05        | 3,8628E-05        | 5,7743E-05   |
| <b>HTR4</b>  | 6,4602E-06  | NA           | NA           | NA           | 5,0793E-05     | 2,8871E-05     | 2,0204E-05     | NA            | 3,9084E-06        | NA                | NA                | 8,9171E-06        | NA           |
| <b>HTR5A</b> | NA          | NA           | NA           | NA           | NA             | NA             | NA             | 4,7951E-06    | NA                | NA                | NA                | NA                | NA           |
| <b>HTR6</b>  | 9,8599E-06  | 0,00002411   | 3,7833E-05   | 1,8021E-05   | 1,3752E-05     | 3,9852E-05     | 1,5962E-05     | 4,7887E-05    | 0,00026166        | 1,5259E-05        | 3,2595E-05        | 0,00003328        | 1,9381E-05   |
| <b>HTR7</b>  | 8,3778E-06  | 2,2526E-06   | 4,664E-06    | 2,284E-06    | 1,1905E-06     | 2,431E-06      | 6,2268E-07     | 5,4063E-05    | 9,1166E-07        | 2,8972E-05        | 1,9474E-06        | 2,5608E-06        | 1,344E-06    |



### Conclusion

These results suggest that the measure of the expression level of *HTR1D* gene(s) might be used in the diagnosis, prognosis and stratification of breast cancer and in particular breast cancer of the luminal, HER-2 enriched and triple negative type. Furthermore, in  
5 view of these results, the treatment of said cancer by the inhibition of 5-HTR1<sub>D</sub> appear as a promising approach.

### **Example 5: effect of the inhibition of 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub> on breast cancer cell lines**

#### Material and Methods

##### 10 Drug treatment

TNBC cell lines were treated with different doses of BRL-15,572 (selective antagonist of 5-HTR1<sub>D</sub>) or GR-127935 (potent and dual antagonist of 5-HTR1<sub>D</sub> and 5-HTR1<sub>B</sub>) for 72h and cell viability was assessed using the CellTiter-Glo® assay from Promega according to according to the manufacturer's protocol.

15 Proliferation assay were performed at 72h with the different compounds indicated using the colorimetric BrDU assay from Cell Signaling. Induction of cell apoptosis were detected after 6 hours of treatment using the RealTime-Glo™ Annexin V Apoptosis assay (Promega).

20 All the experiments were done in three independent replicates and relatively compared to the vehicle control. Values are expressed as means and standard deviation (SD). Statistical analysis (Student's t-test was conducted using Graphpad Prism software version 7.0 and the difference was considered significant when \*p < 0.05.

#### siRNA experiments

25 Cells were transfected with 50 (siRNA Ctrl, siRNA HTR1<sub>D</sub>) or 100 nM siRNA (SiRNA Ctrl and SiRNA HTR1<sub>B</sub>+HTR1<sub>D</sub> in the presence of Dhermafect I reagent (Dharmacon), in accordance with the manufacturer's protocol. All siRNAs were purchased from

Dharmacon. Cell viability was assessed with the CellTiter-Glo assay (Promega) 120 h after transfection.

### Results

5 Treatment of triple negative cancer cell lines with BRL-15,572 comprised their viability in a dose-dependent manner (**Fig. 30A**). Treatment of cells from the BT549 triple negative cancer cell line with BRL-15,572 induced their apoptosis and inhibited their proliferation in a dose-dependent manner (**Fig. 30B-C**).

10 Treatment of triple negative cancer cell lines with GR-127935 comprised their viability in a dose-dependent manner (**Fig. 31A**). Treatment of cells from the BT549 triple negative cancer cell line with GR-127935 induced their apoptosis and inhibited their proliferation in a dose-dependent manner (**Fig. 31B-C**).

Silencing the expression of *HTR1D* in BT549 cells compromised their viability (**Fig. 32**). The silencing of both *HTR1D* and *HTR1B* lead to a stronger decrease of BT549 cell viability (**Fig. 32**).

### 15 Conclusion

These results suggest the use of 5-HTR<sub>1D</sub> inhibitors alone or in combination with 5-HTR<sub>1B</sub> inhibitors in the treatment of cancer, in particular breast cancer and triple negative breast cancer.

## CLAIMS

1. A 5-hydroxytryptamine receptor 1D (5-HTR<sub>1D</sub>) inhibitor, for use in the prevention and/or treatment of cancer in a subject in need thereof.
- 5 2. The 5-HTR<sub>1D</sub> inhibitor of claim 1, wherein said 5-HTR<sub>1D</sub> inhibitor is selected from the group comprising small organic molecules, antibodies, aptamers and polynucleotides.
3. The 5-HTR<sub>1D</sub> inhibitor for use according to claim 1 or 2, wherein said 5-HTR<sub>1D</sub> inhibitor is a selective 5-HTR<sub>1D</sub> inhibitor.
- 10 4. A combination of a 5-HTR<sub>1D</sub> inhibitor and at least one inhibitor of 5-hydroxytryptamine receptor 1B (5-HTR<sub>1B</sub>) for use in the prevention and/or treatment of cancer in a subject in need thereof wherein said 5-HTR<sub>1D</sub> inhibitor and/or 5-HTR<sub>1B</sub> is preferably selected from the group comprising small organic molecules, antibodies, aptamers and polynucleotides.
- 15 5. A composition for use in the prevention and/or treatment of cancer in a subject in need thereof, comprising a 5-HTR<sub>1D</sub> inhibitor according to any one of claims 1 to 3.
6. The composition for use according to claim 5 further comprising at least one inhibitor of 5-hydroxytryptamine receptor 1B (5-HTR<sub>1B</sub>).
7. The composition for use according to claim 6, wherein said 5-HTR<sub>1B</sub> inhibitor is  
20 selected from the group comprising small organic molecules, antibodies, aptamers and polynucleotides.
8. The composition for use according to any one of claims 5 to 7 being a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient.
- 25 9. The 5-HTR<sub>1D</sub> inhibitor for use according to any one of claims 1 to 3, the combination for use according to claim 4, the composition for use according to any one of claims 5 to 8, wherein said cancer is selected from the group comprising

breast cancer, liver cancer, lung cancer, brain cancer, mesothelioma, head and neck squamous cell carcinoma, kidney cancer, gastric cancer and cervix cancer.

- 5       **10.**   The 5-HTR1<sub>D</sub> inhibitor for use, the combination for use or the composition for use according to any one of claims **1** to **9**, wherein said cancer is selected from the group comprising breast cancer, liver cancer, lung cancer, brain cancer and mesothelioma.
- 11.**   The 5-HTR1<sub>D</sub> inhibitor for use, the combination for use or the composition for use according to any one of claims **1** to **10**, wherein cancer cells overexpress the gene coding for 5-HTR1<sub>D</sub>.
- 10       **12.**   The 5-HTR1<sub>D</sub> inhibitor for use, the combination for use or the composition for use according to any one of claims **1** to **11**, wherein cancer cells overexpress the gene coding for 5-HTR1<sub>B</sub>.
- 13.**   The 5-HTR1<sub>D</sub> inhibitor for use, the combination for use or the composition for use according to any one of claims **1** to **12**, wherein said cancer is breast cancer preferably triple negative, HER2-enriched, luminal B or luminal A breast cancer.
- 15       **14.**   A medicament comprising the 5-HTR1<sub>D</sub> inhibitor according to any one of claims **1** to **3**, the combination according to claim **4**, the composition according to any one of claims **5** to **8**, for use according to any one of claims **10** to **13**.
- 15.**   An *in vitro* cancer diagnosis, stratification and/or prognosis method comprising a step of measuring the expression level of 5-HTR1<sub>D</sub> and/or 5-HTR1<sub>B</sub> in a sample  
20       previously obtained from a subject.

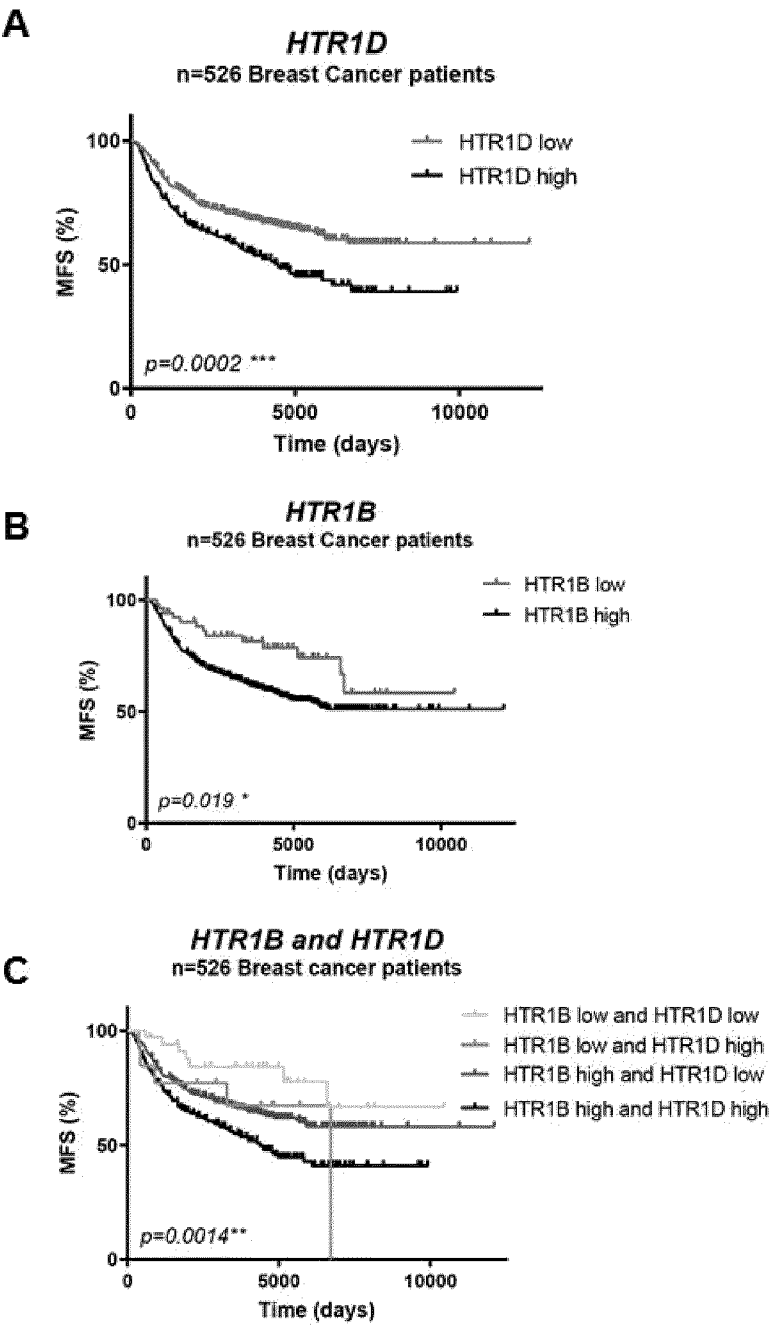


FIG. 1

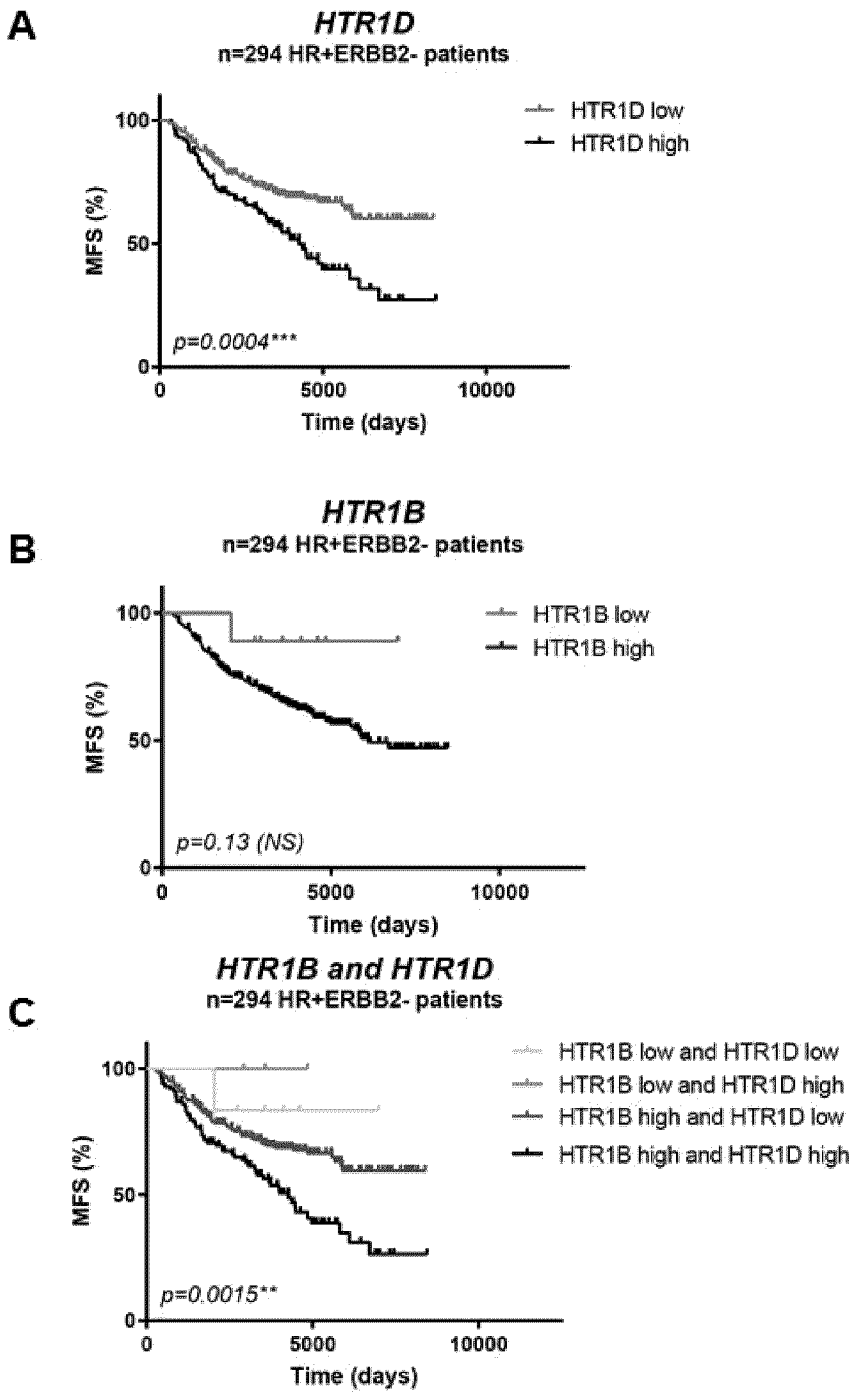


FIG. 2

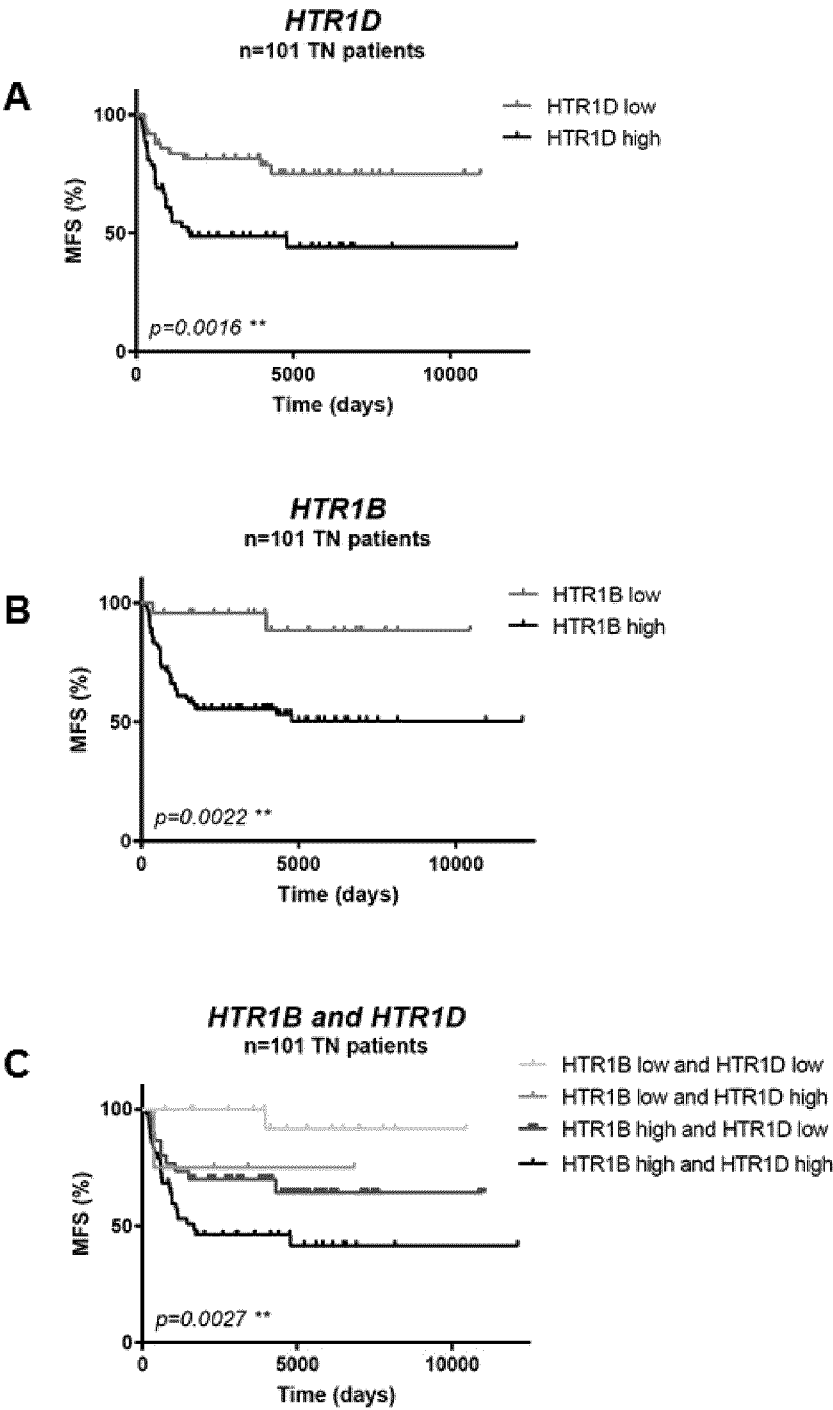


FIG. 3

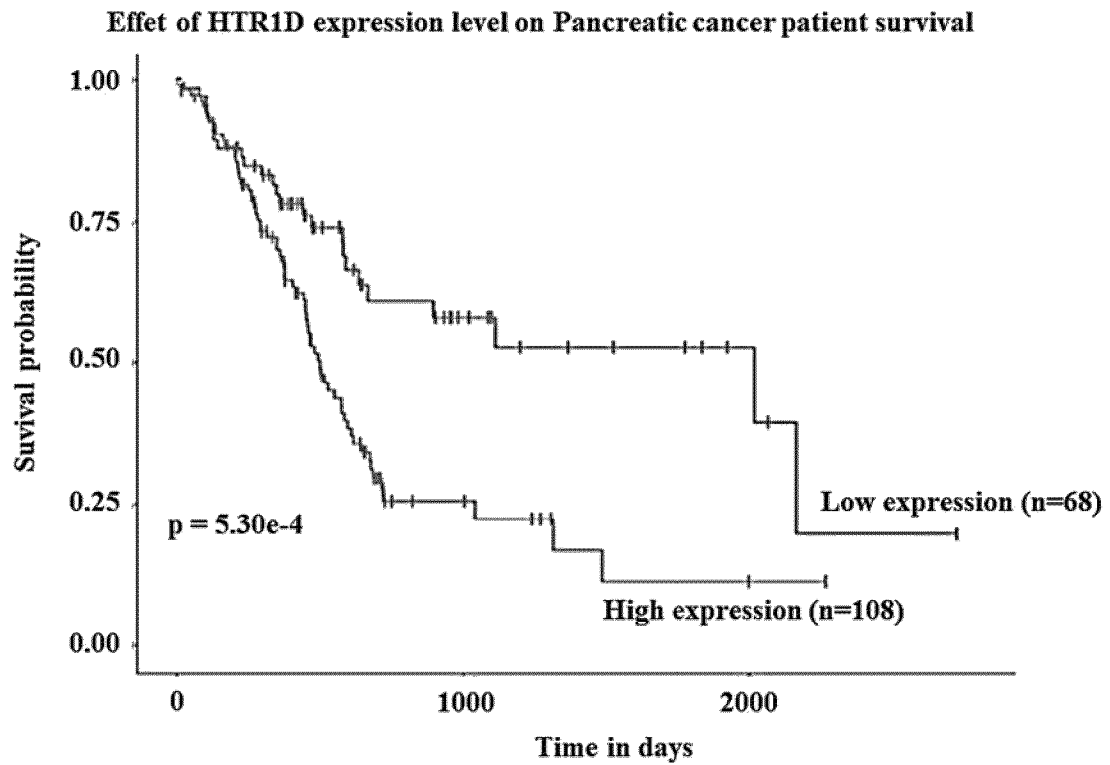


FIG. 4



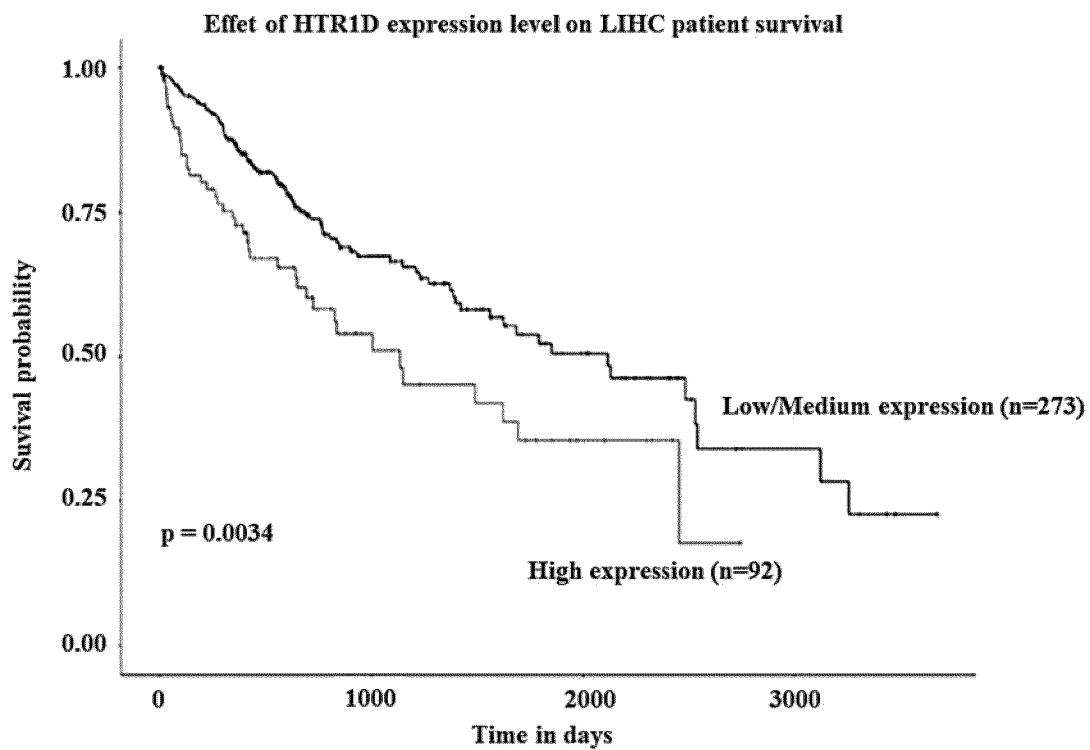


FIG. 5

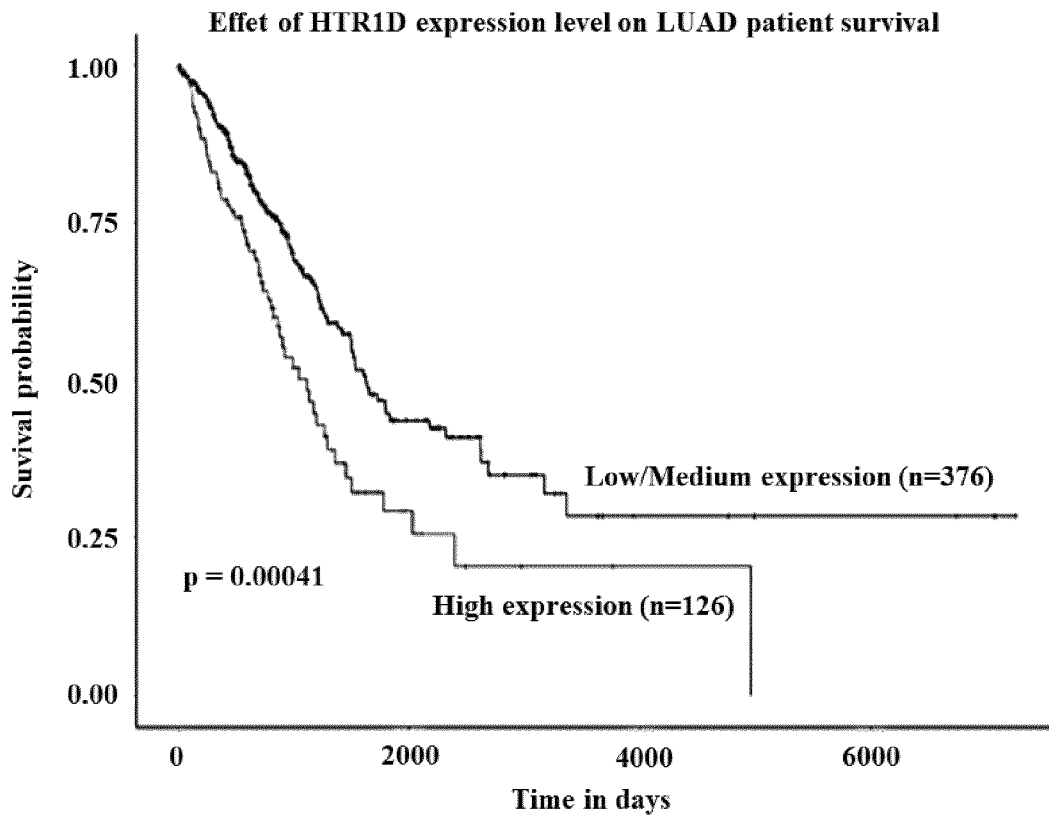


FIG. 6

7/37

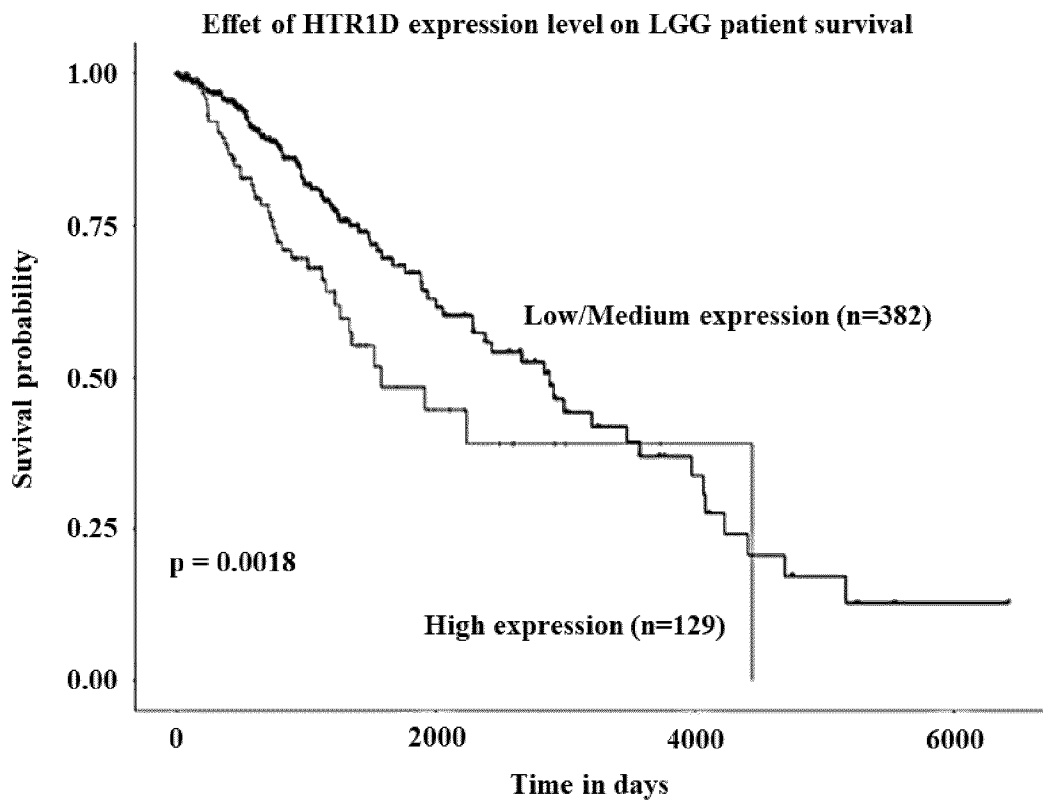


FIG. 7

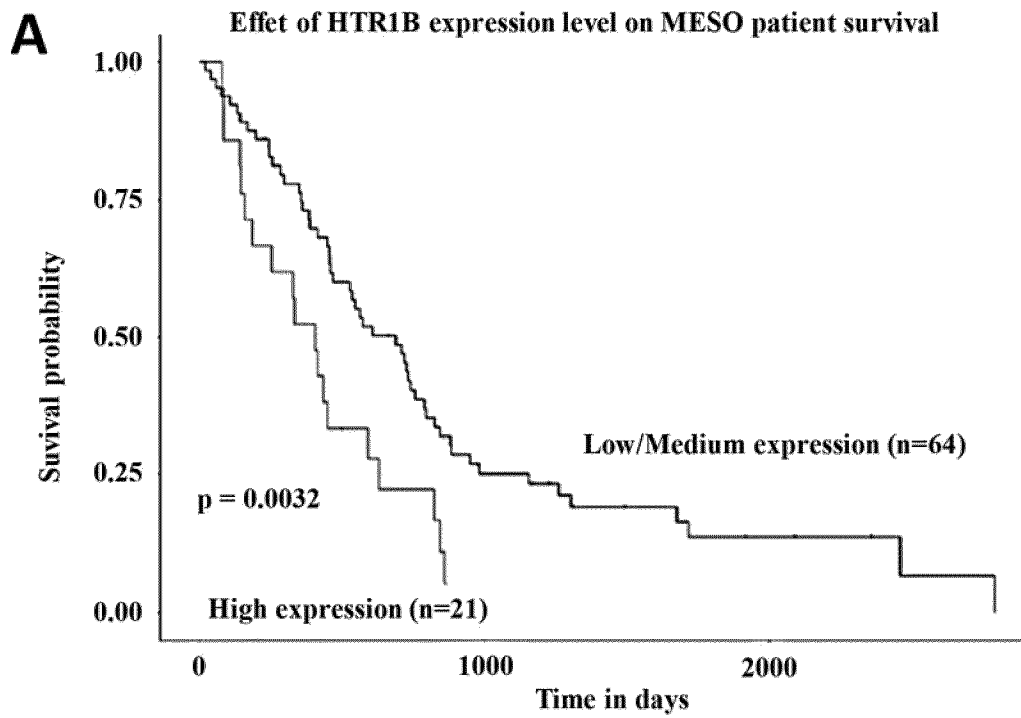


FIG. 8A

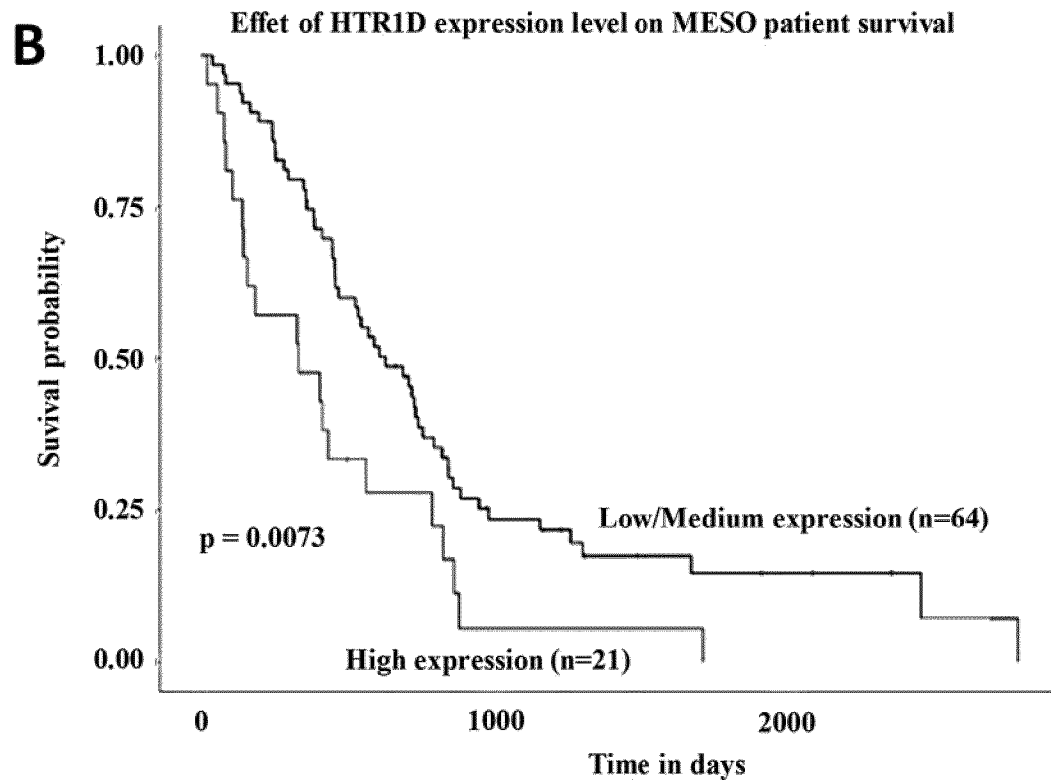


FIG. 8B

10/37

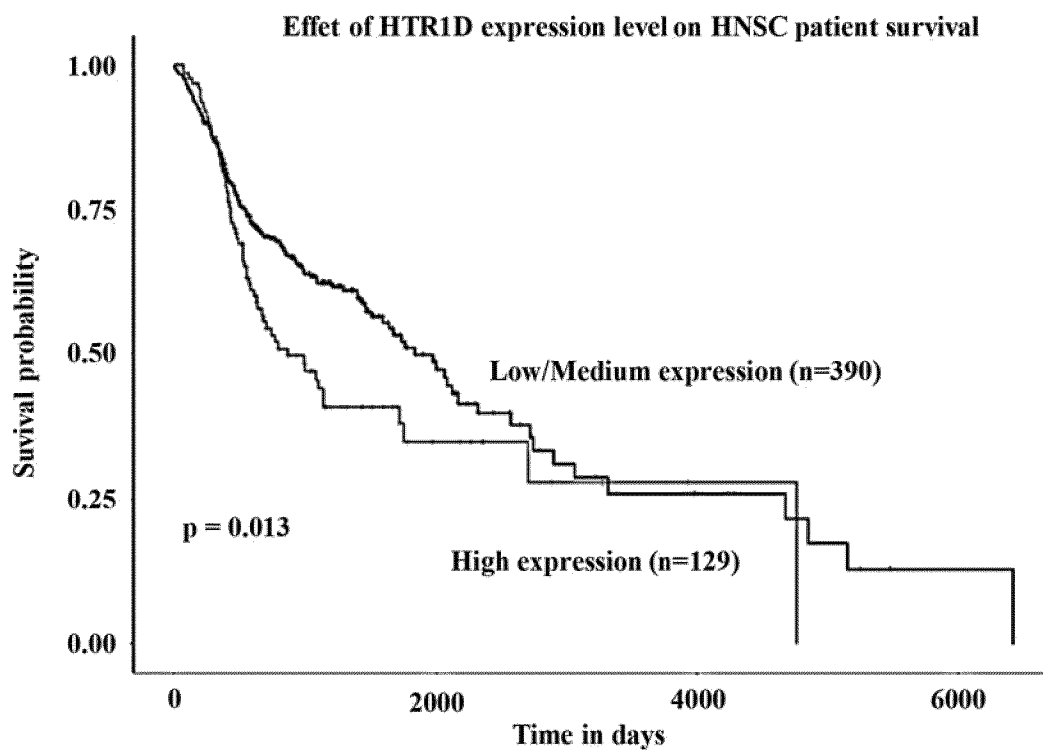


FIG. 9

11/37

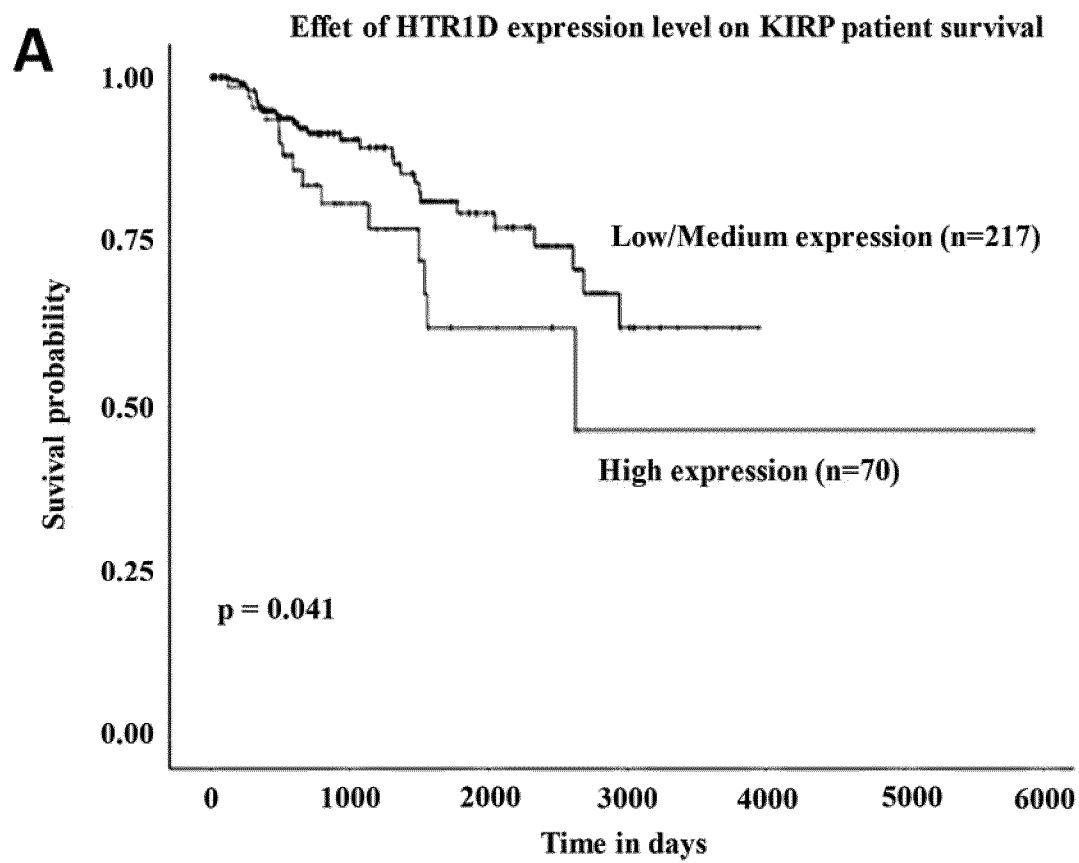


FIG. 10A

12/37

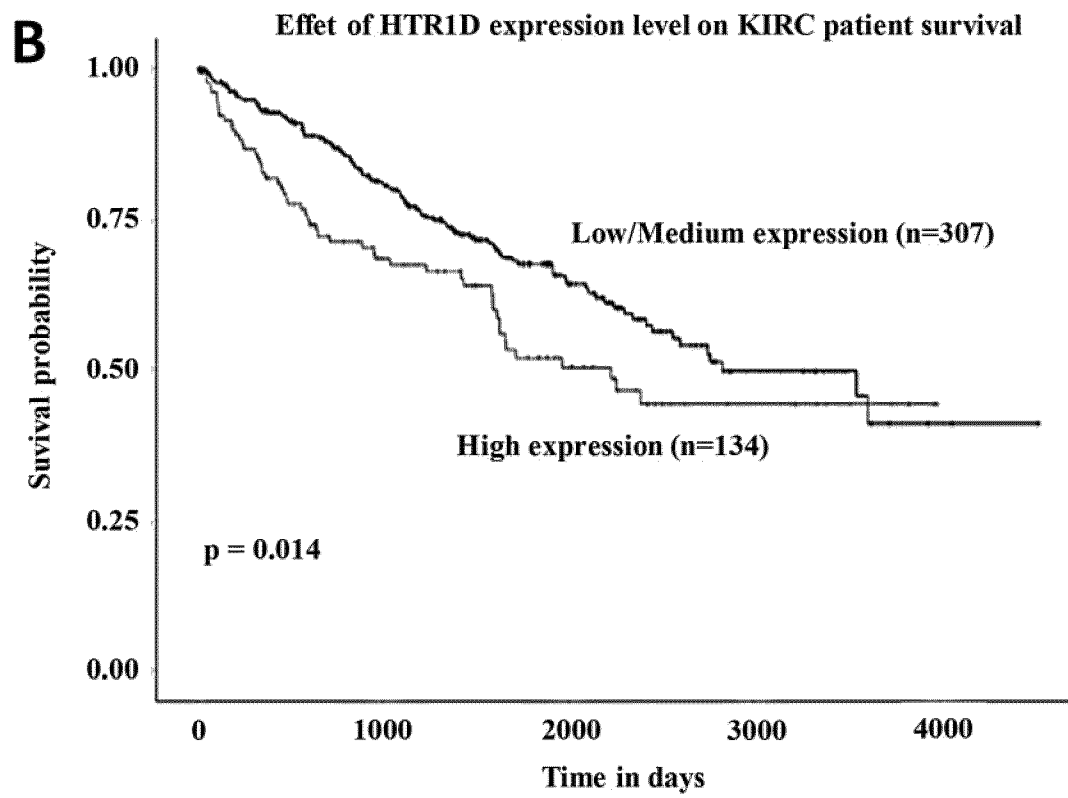


FIG. 10B



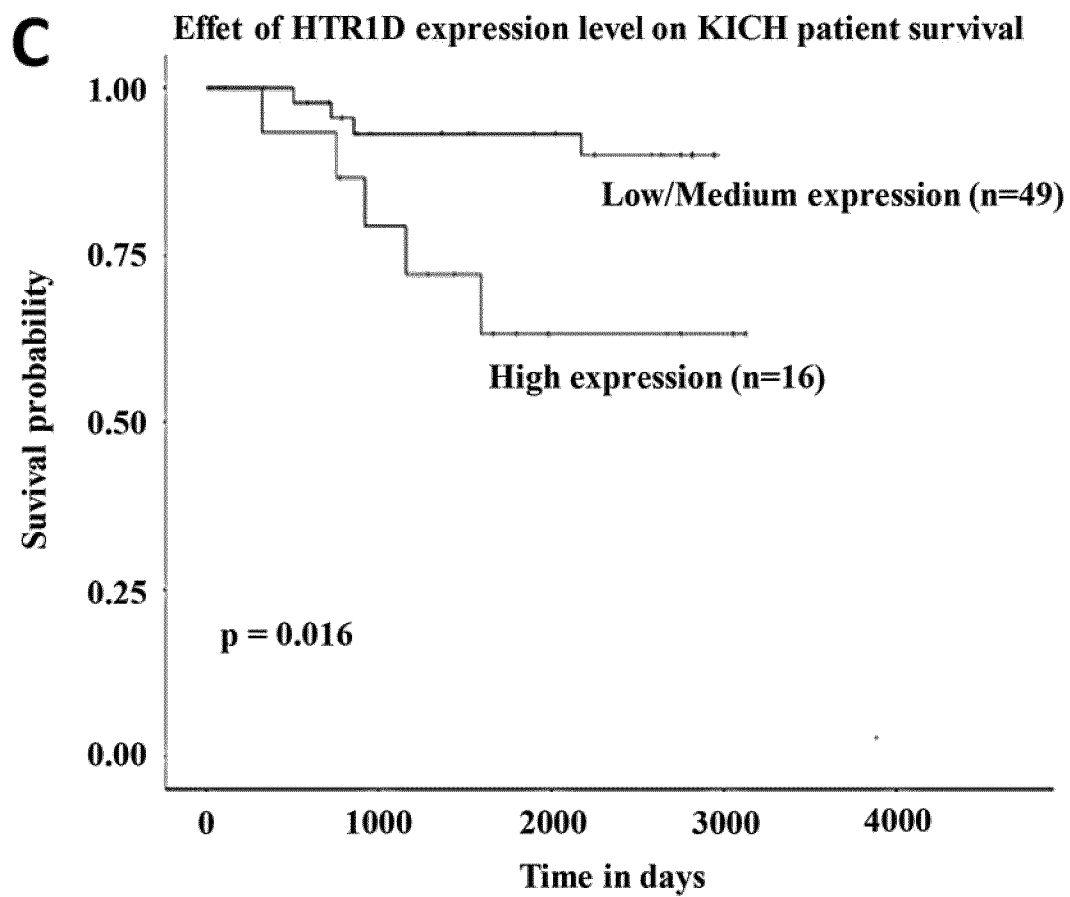


FIG. 10C

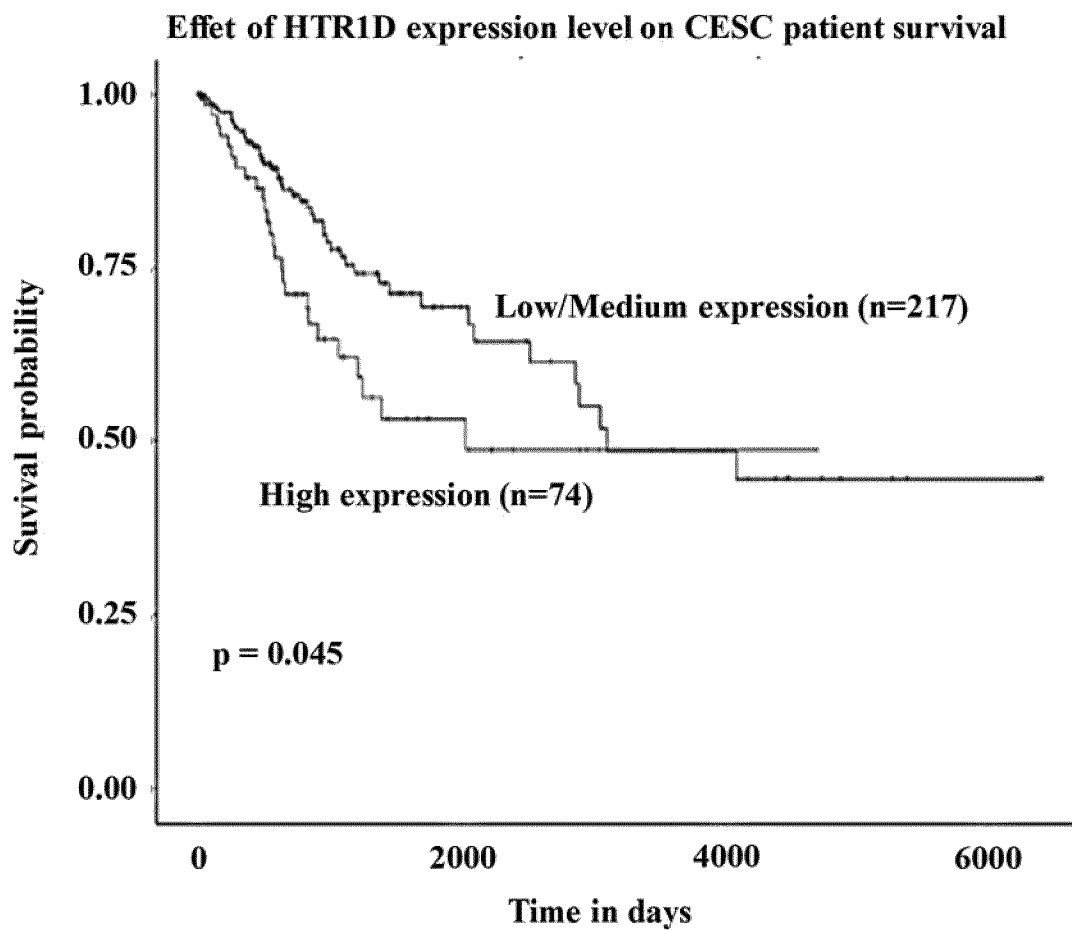


FIG. 11

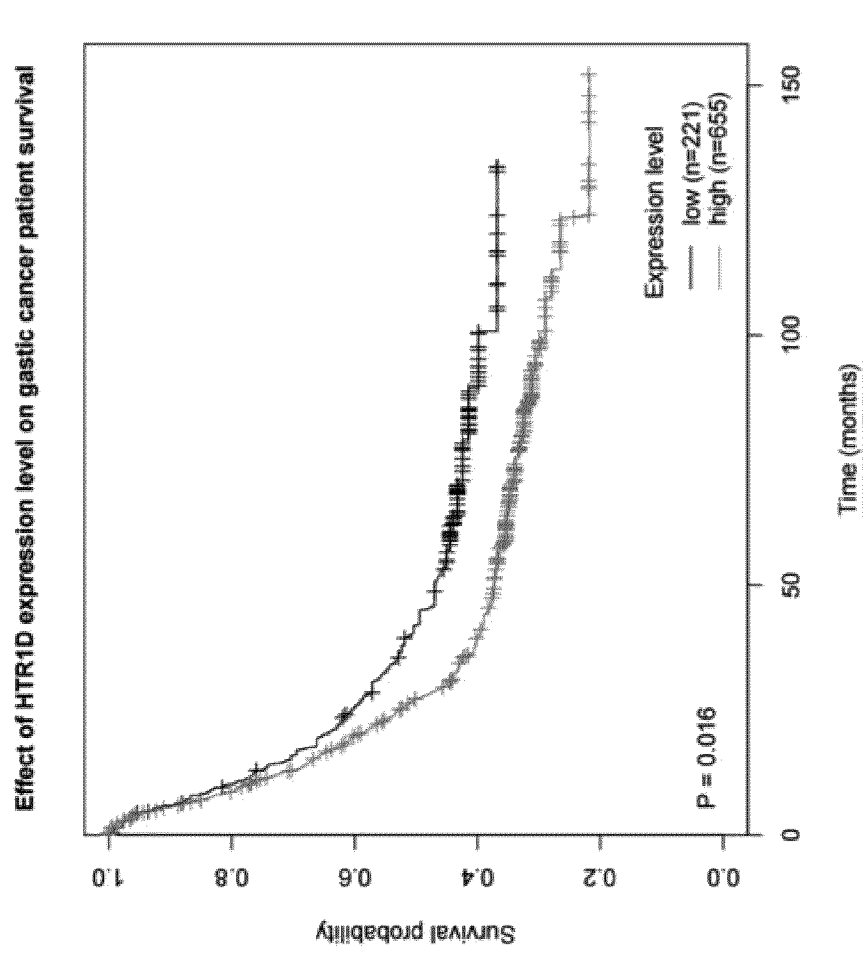


FIG. 12

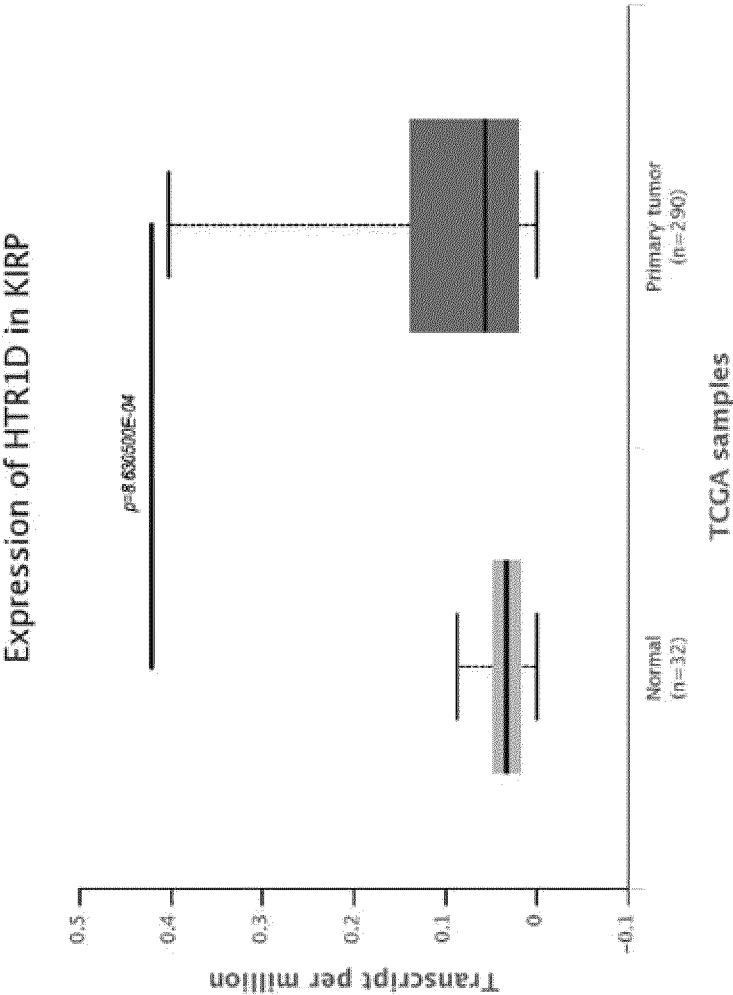


FIG. 13

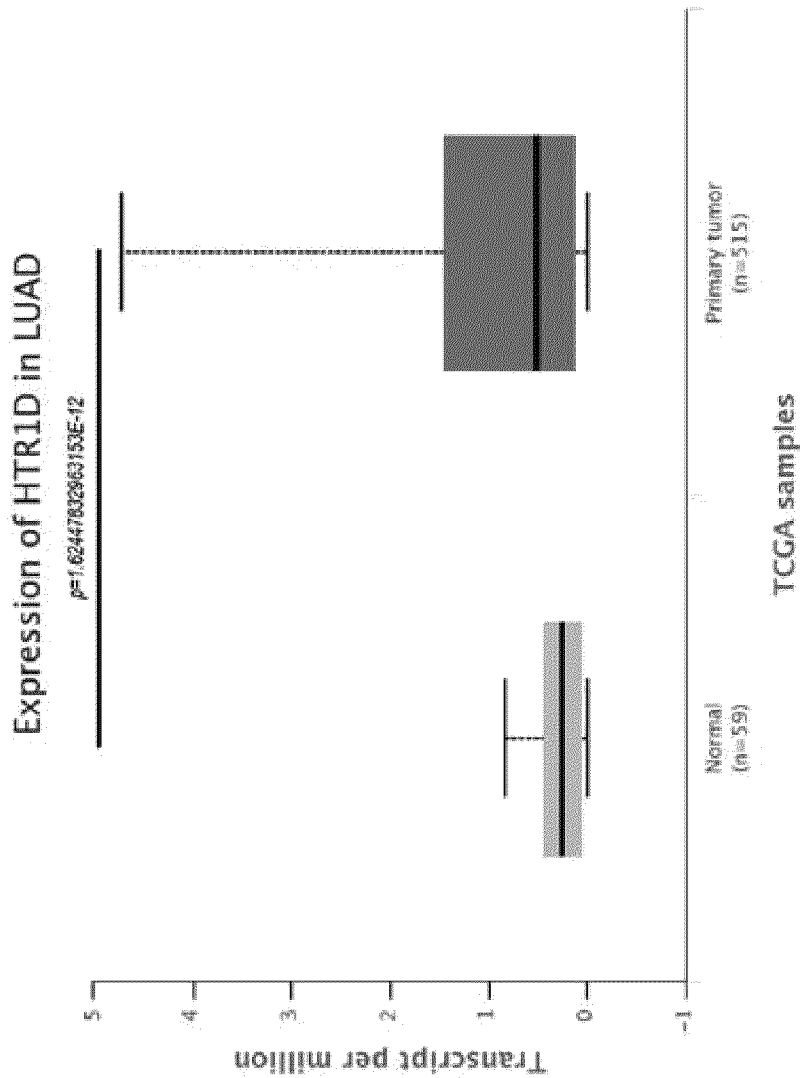


FIG. 14

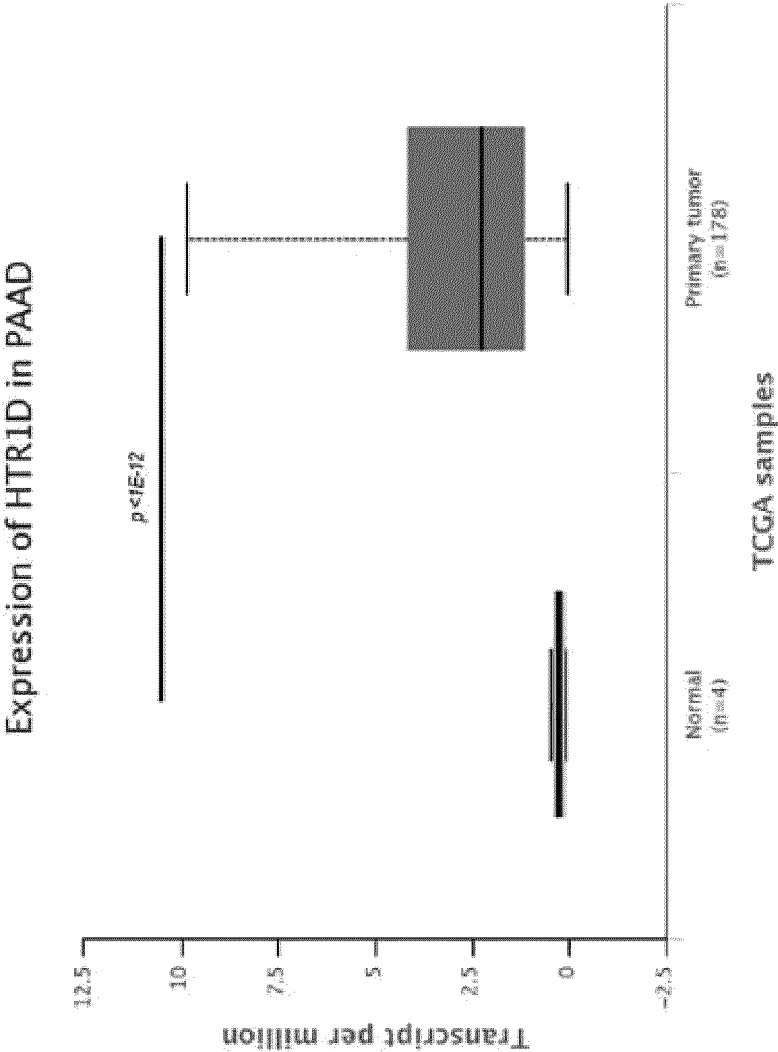


FIG. 15

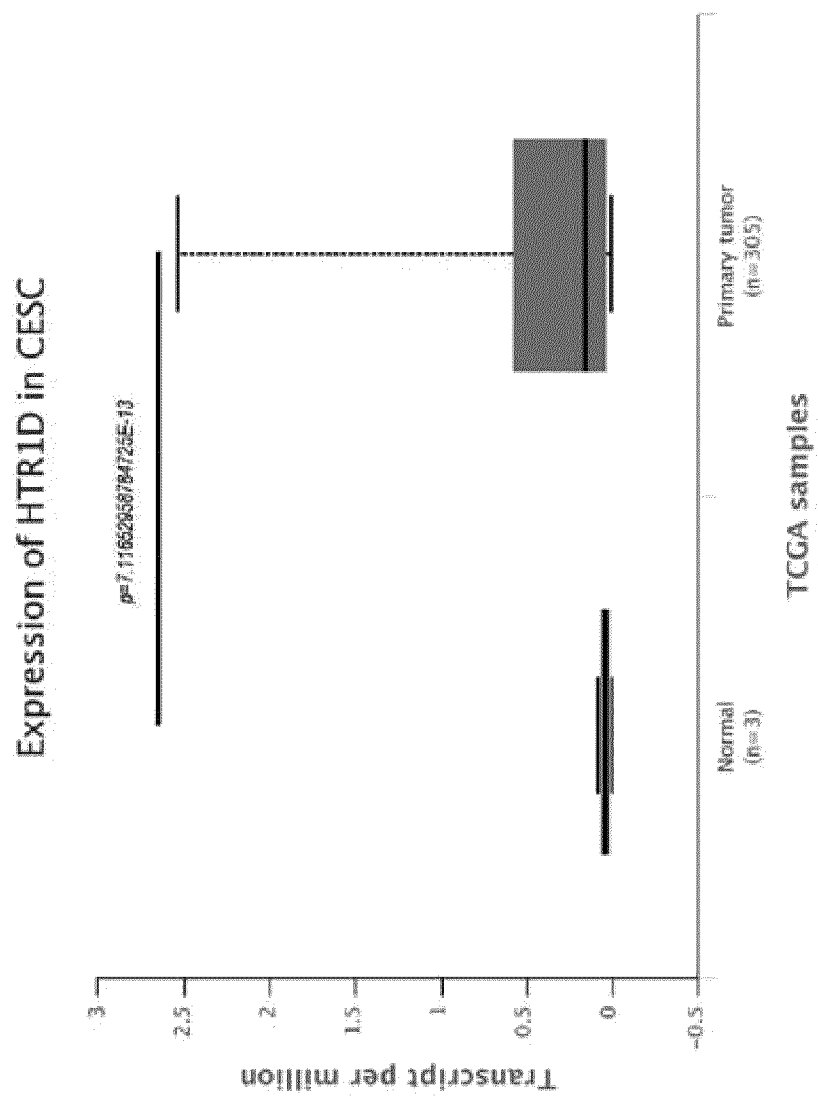


FIG. 16

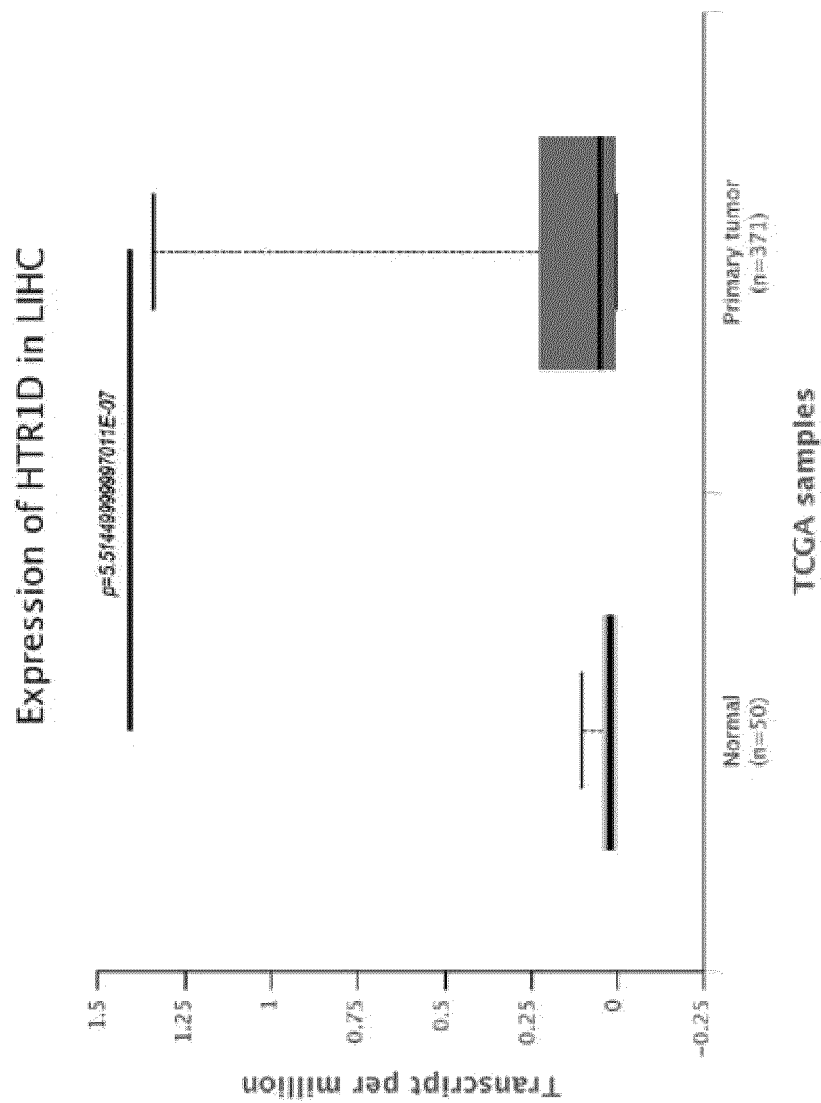


FIG. 17



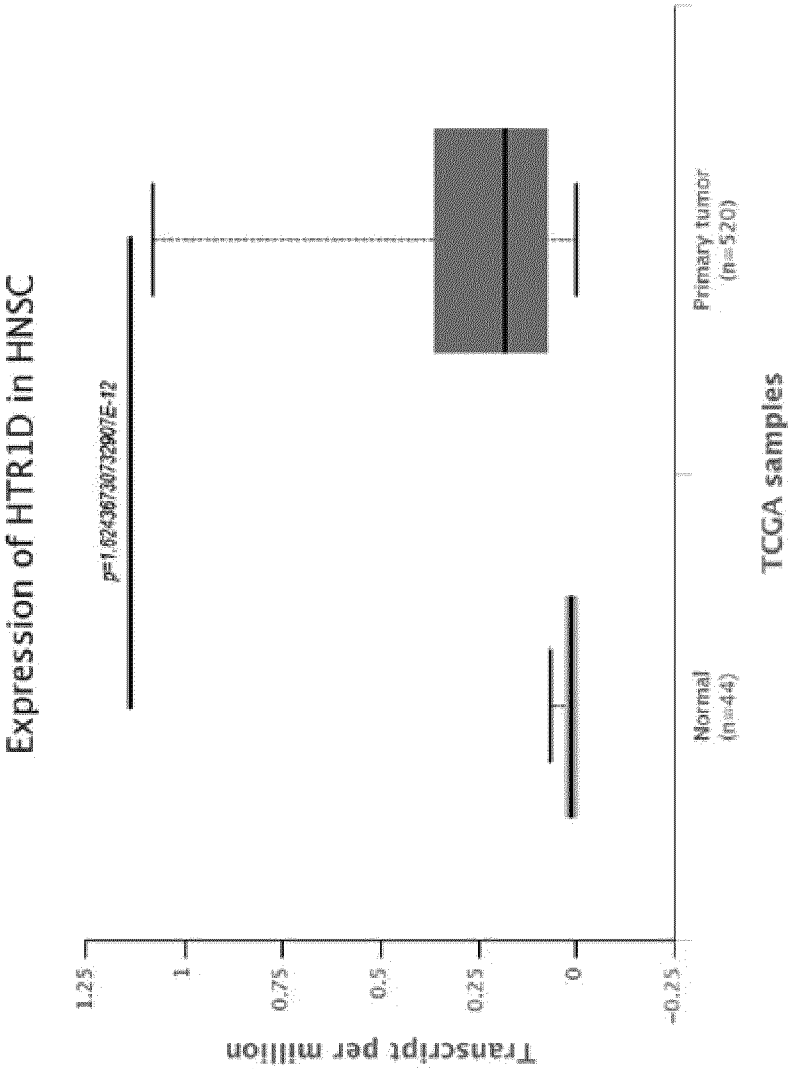


FIG. 18

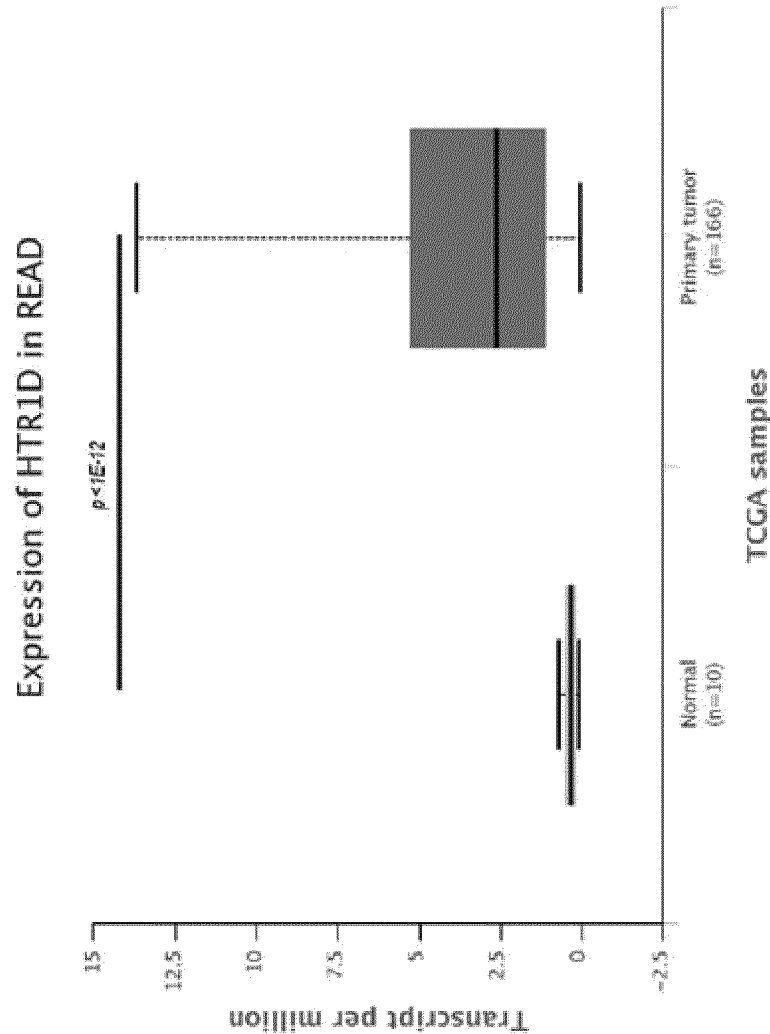


FIG. 19

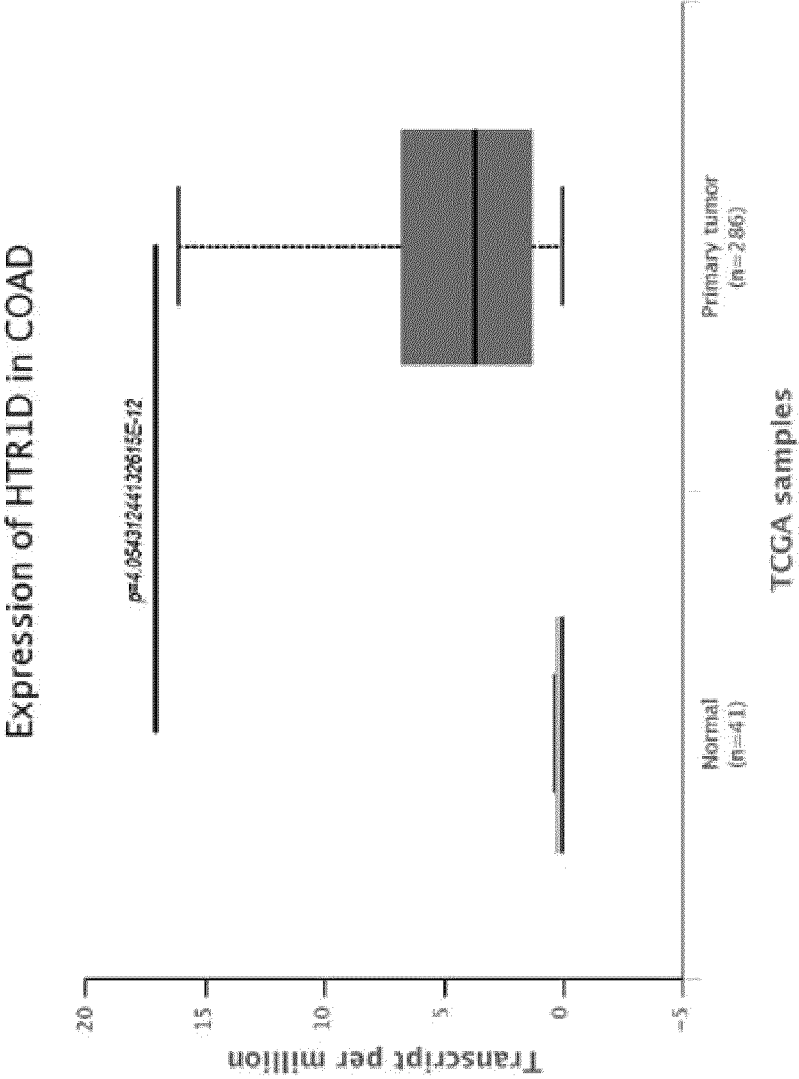


FIG. 20

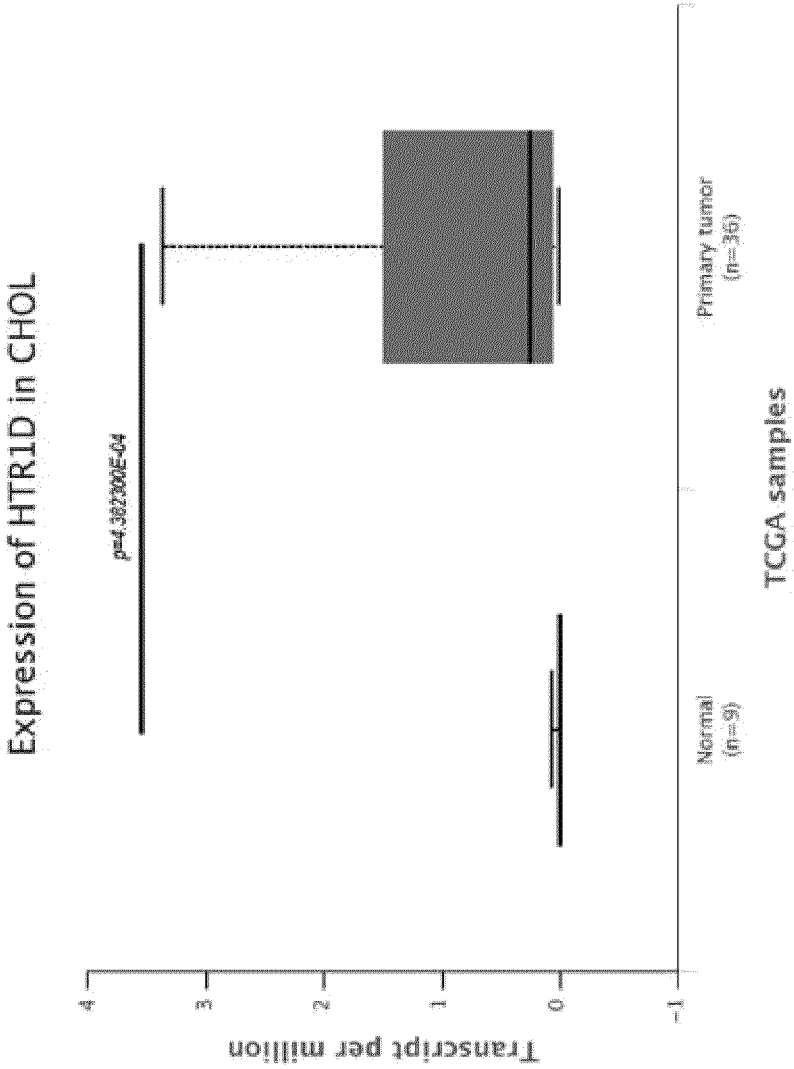


FIG. 21

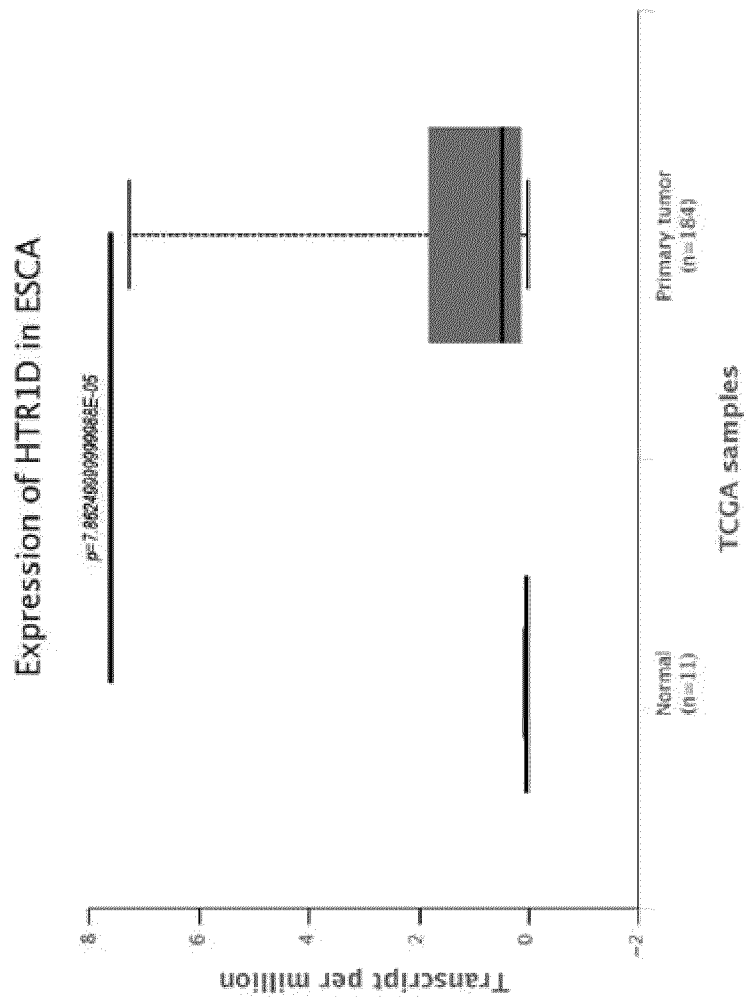


FIG. 22

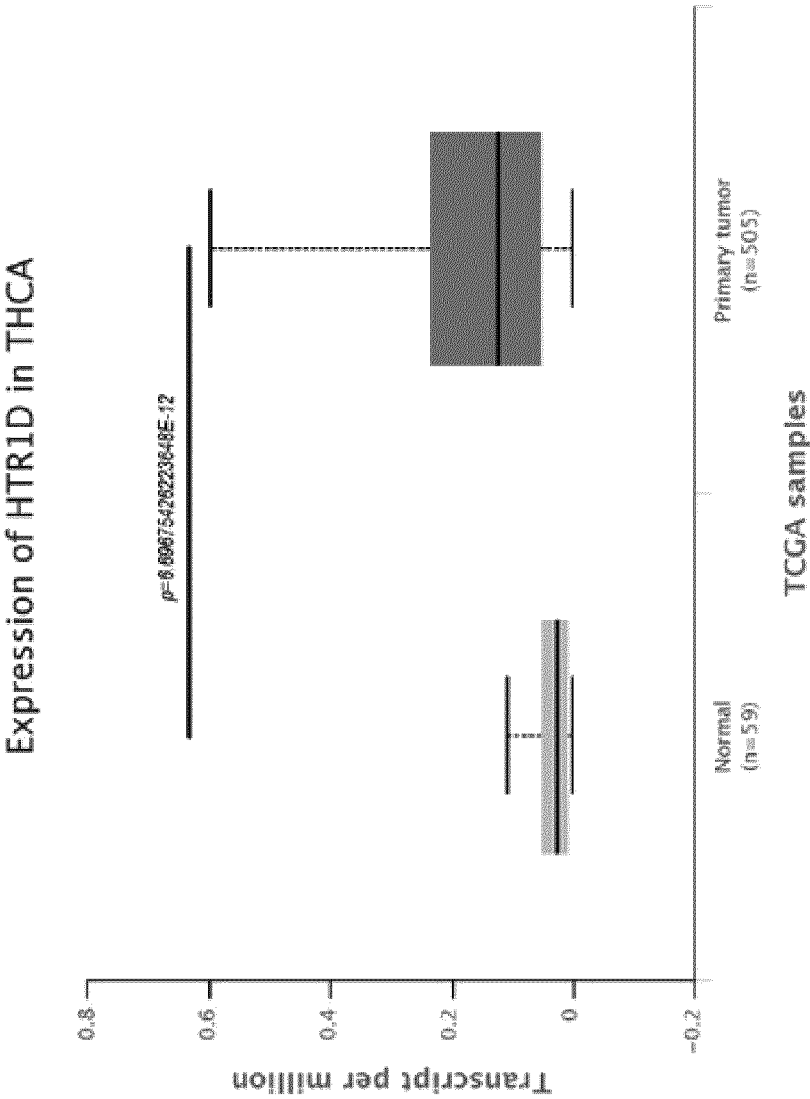


FIG. 23

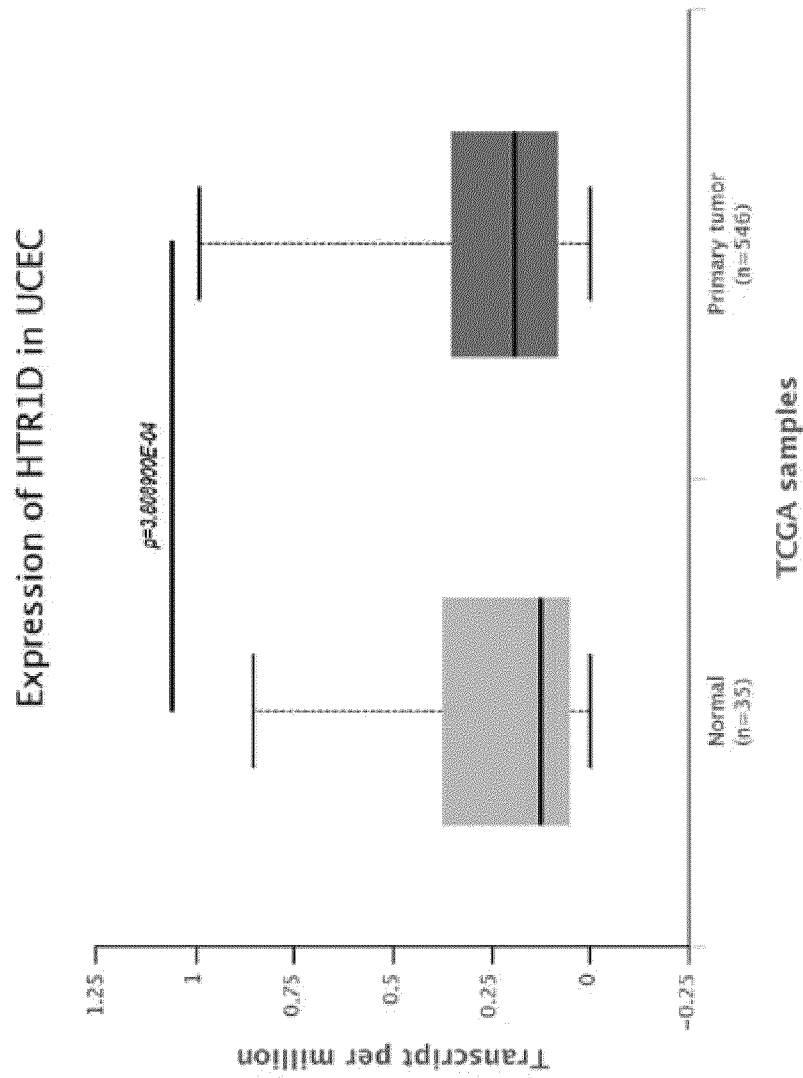


FIG. 24

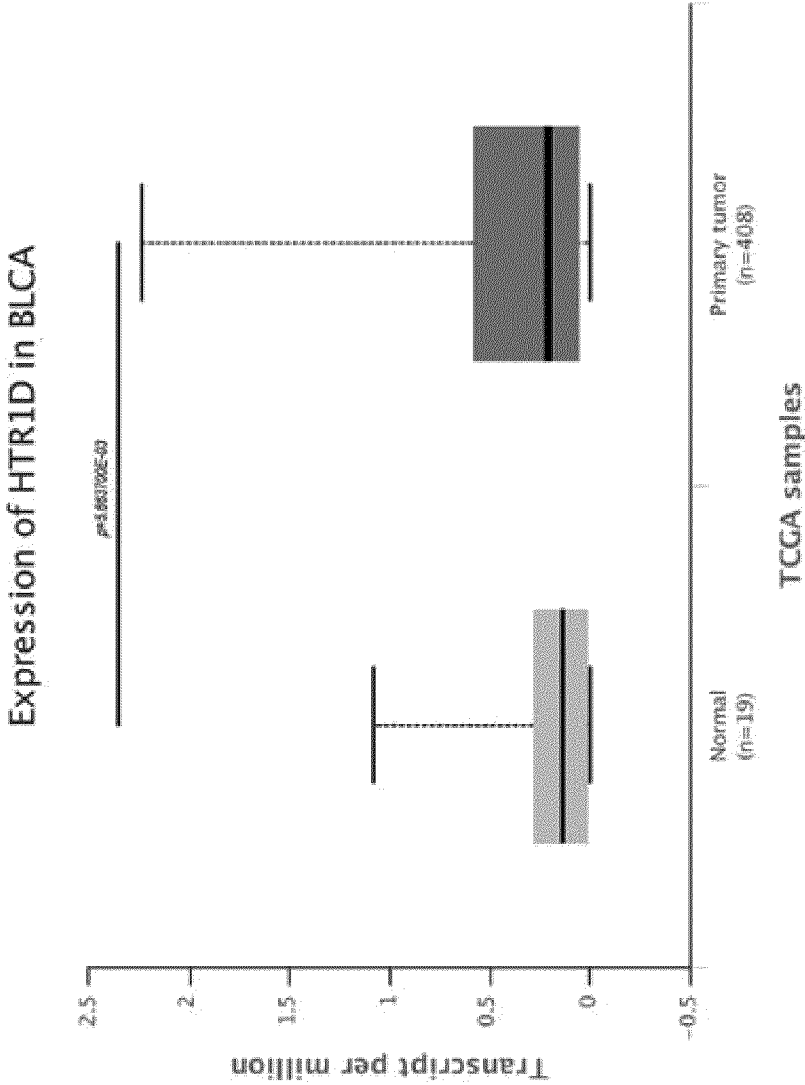


FIG. 25



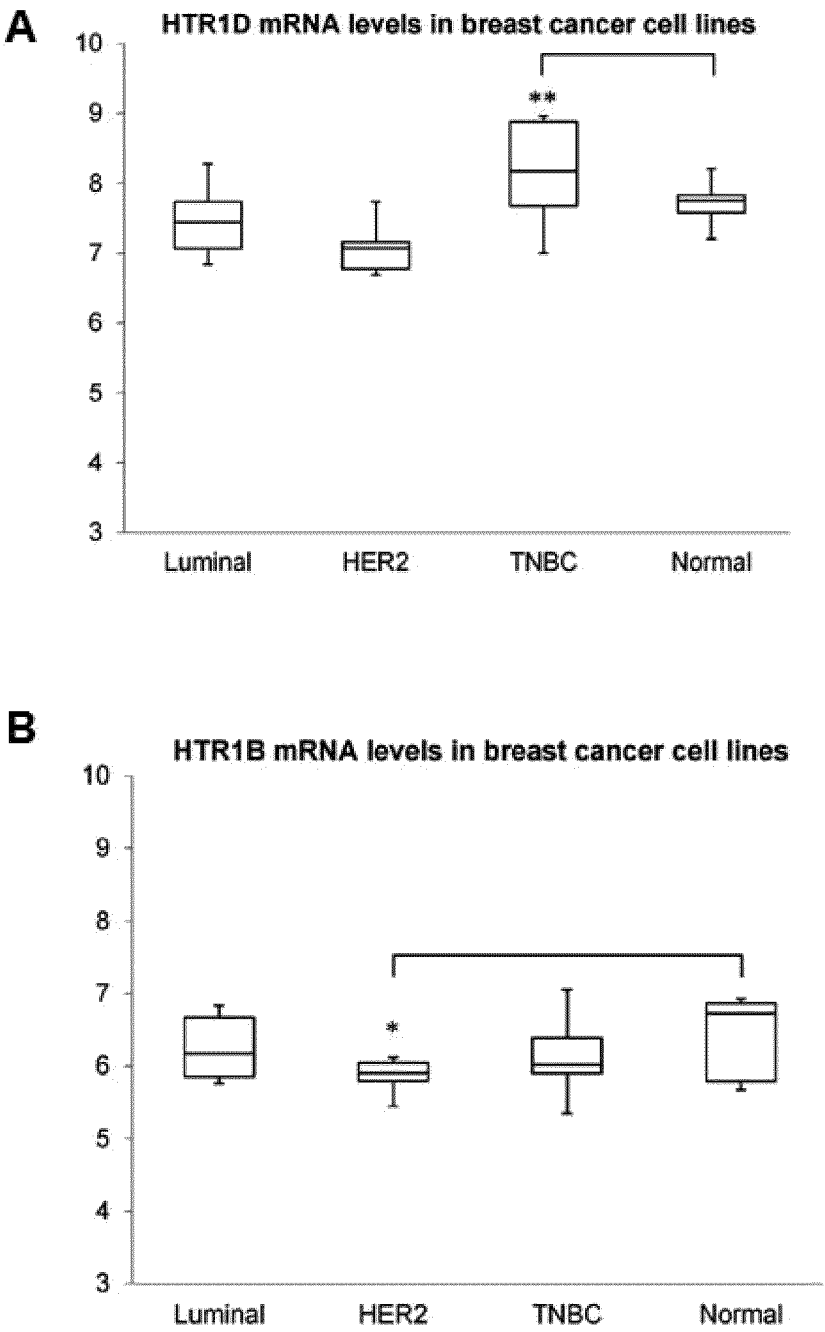


FIG. 26

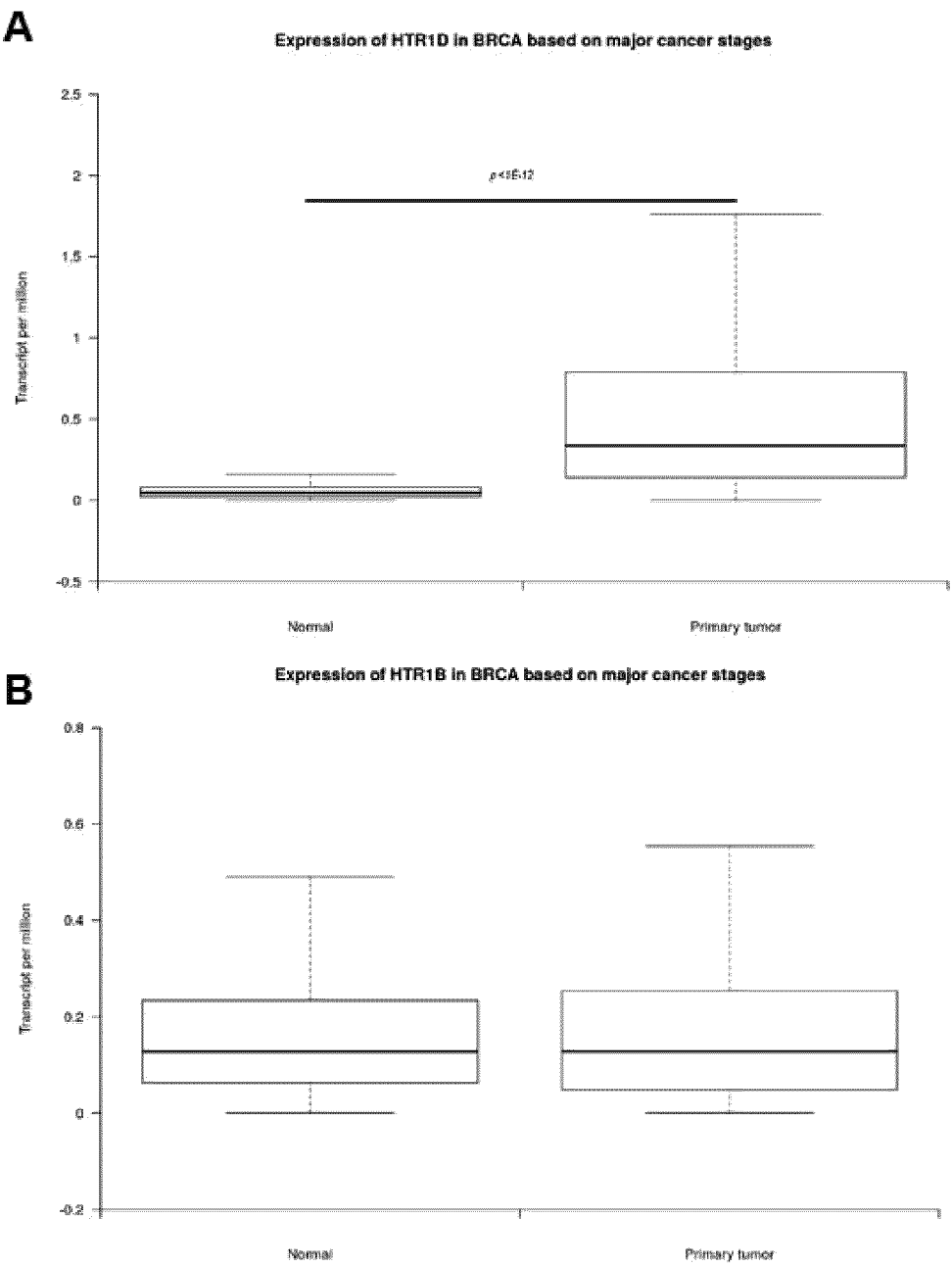


FIG. 27

31/37

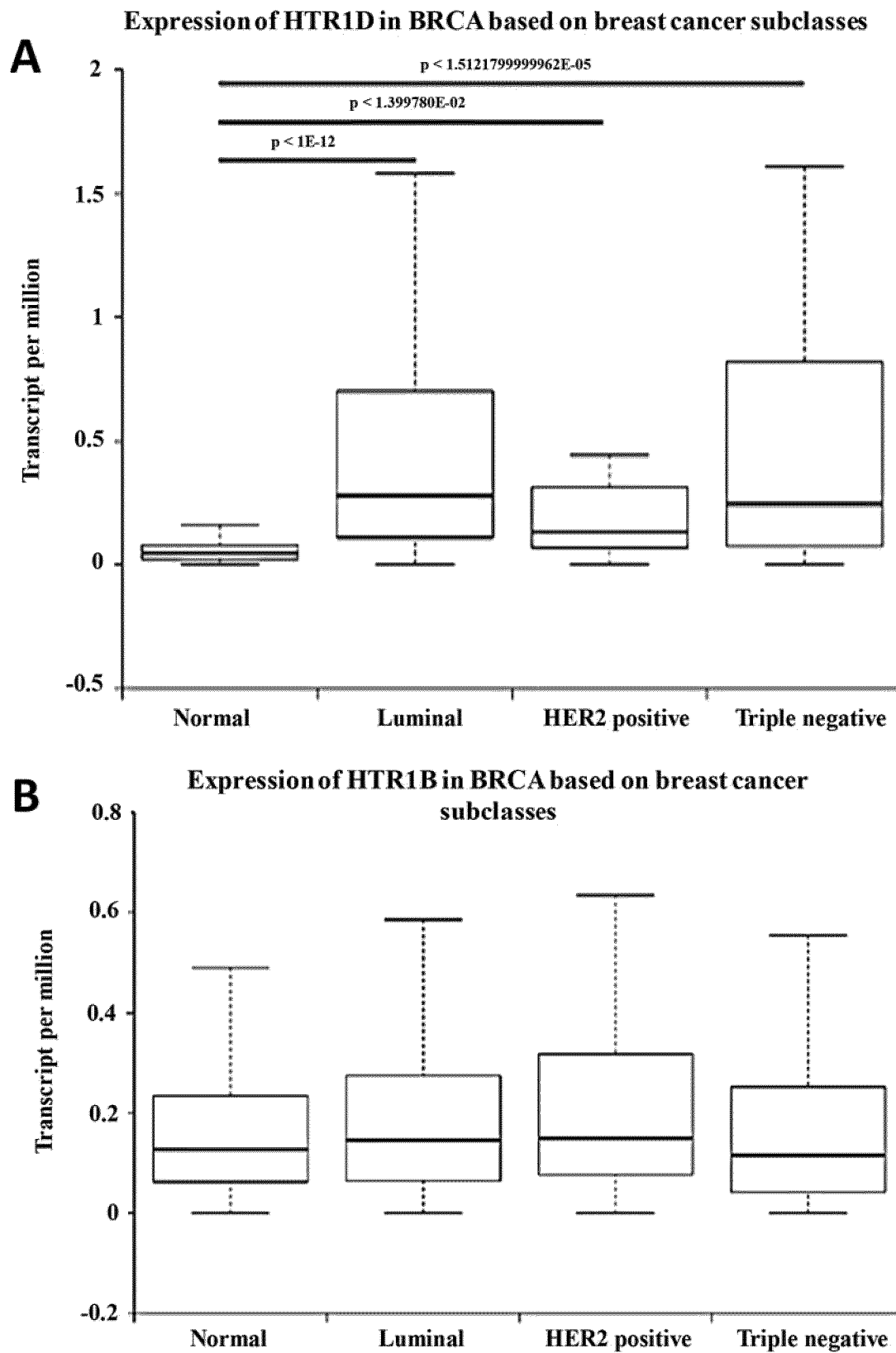


FIG. 28

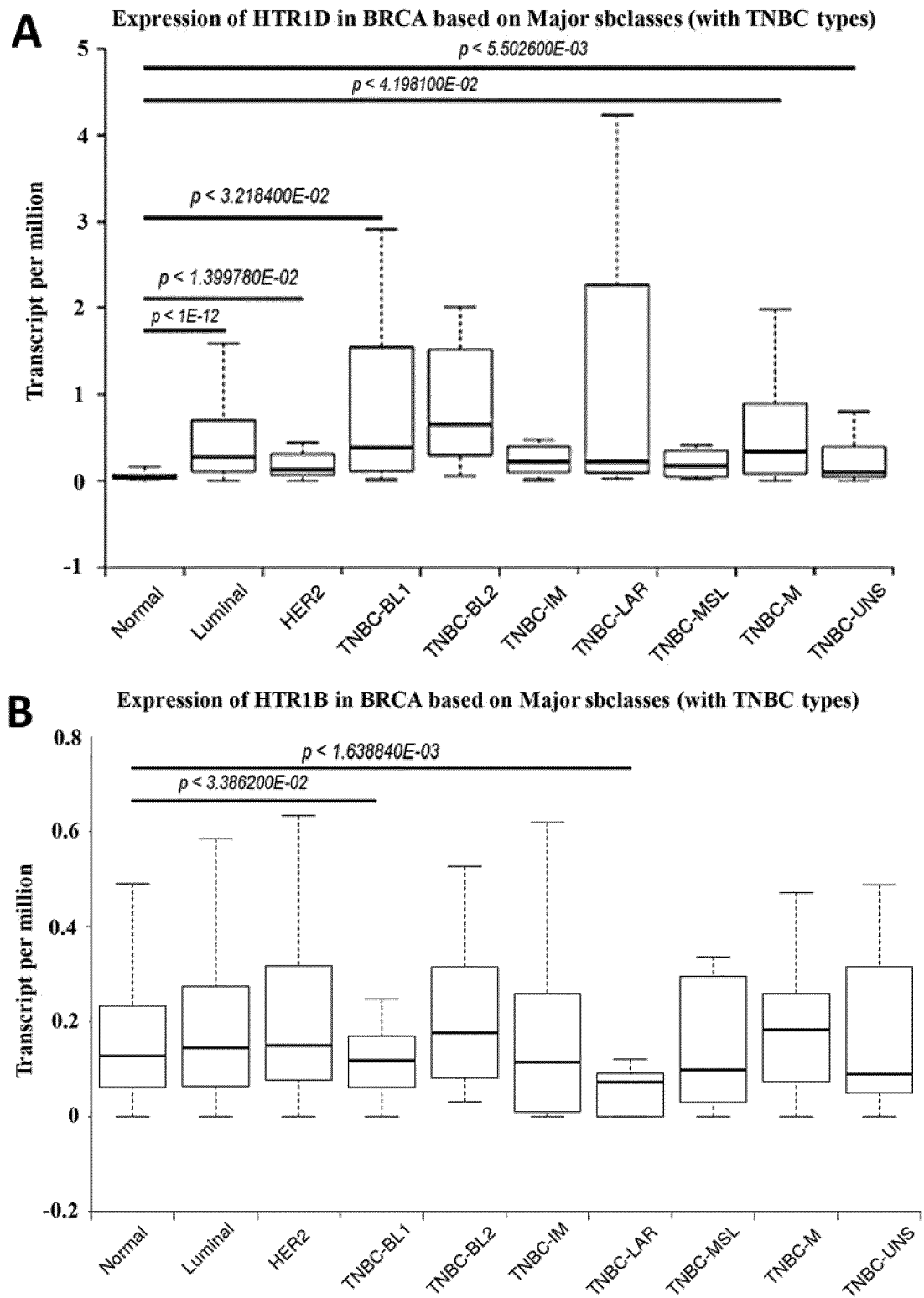


FIG. 29

A

Triple negative breast cancer cell lines viability upon BRL15572 treatment

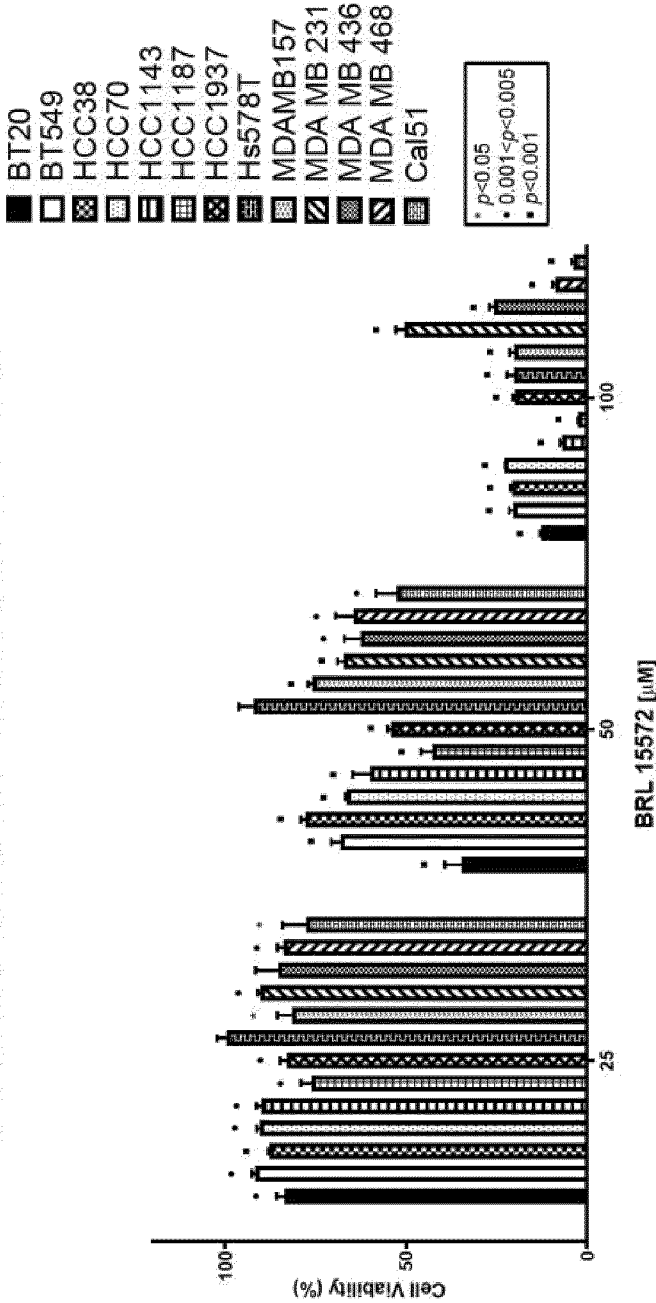


FIG. 30A

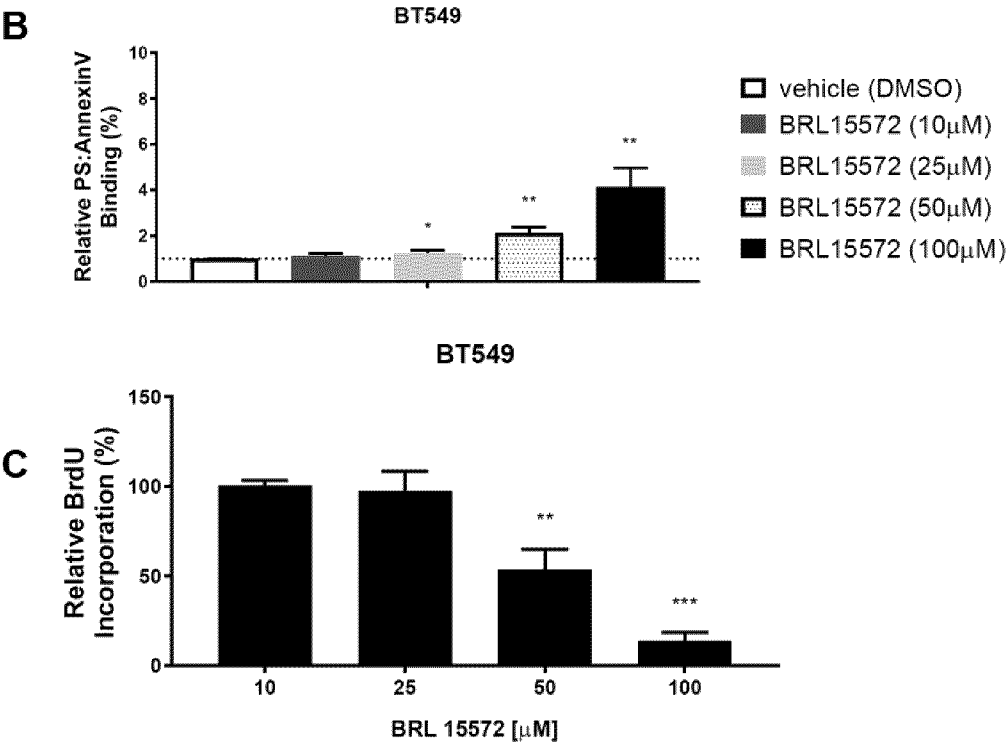


FIG. 30B-C

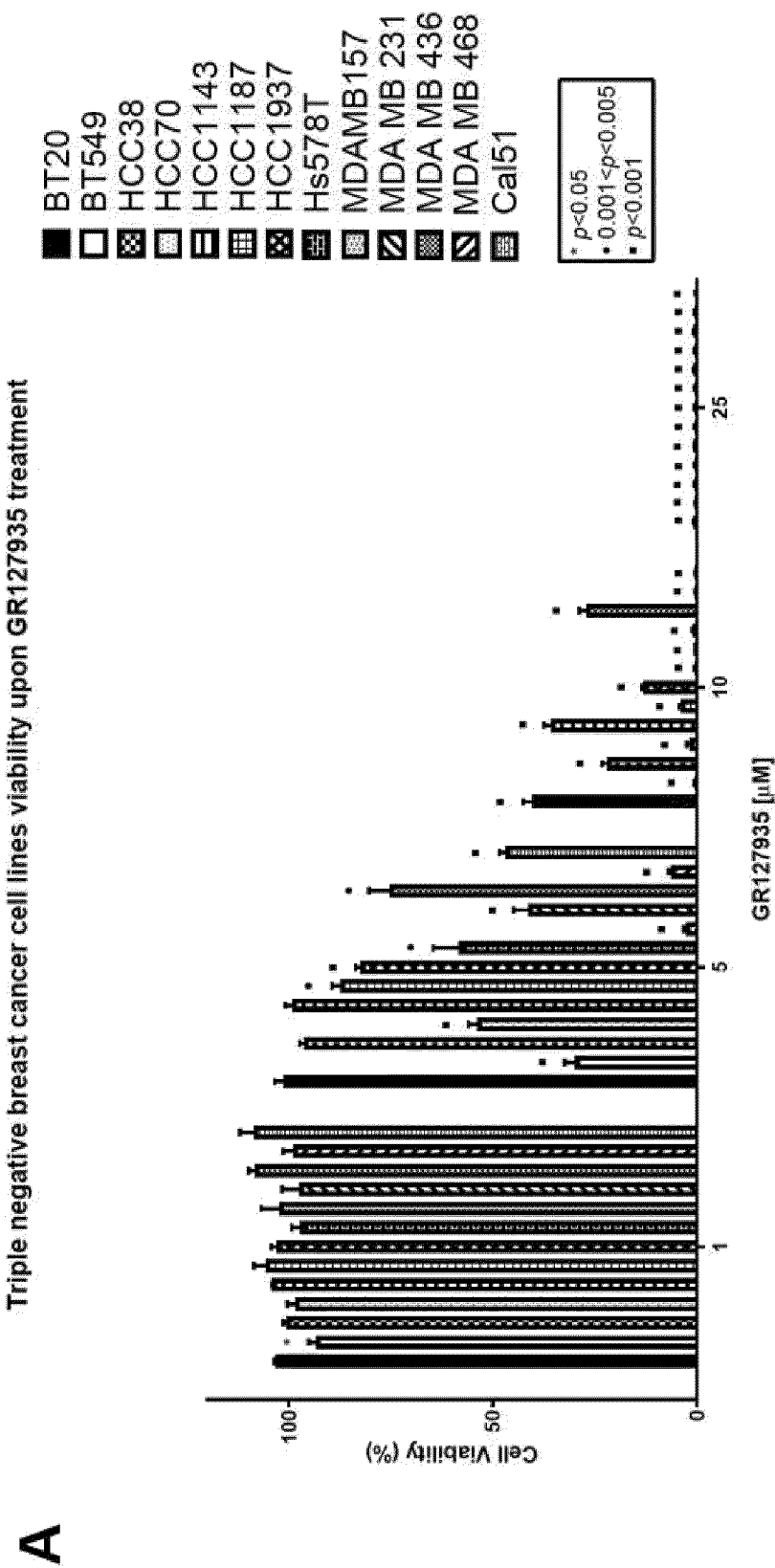


FIG. 31A

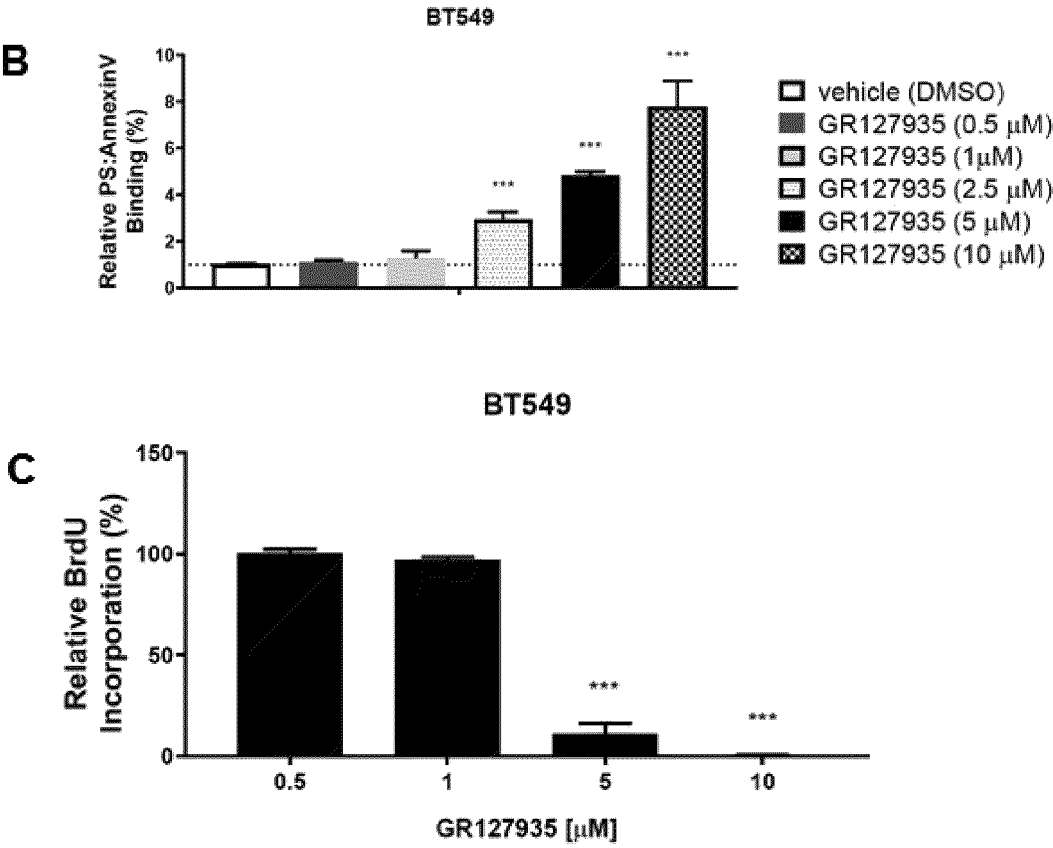


FIG. 31B-C



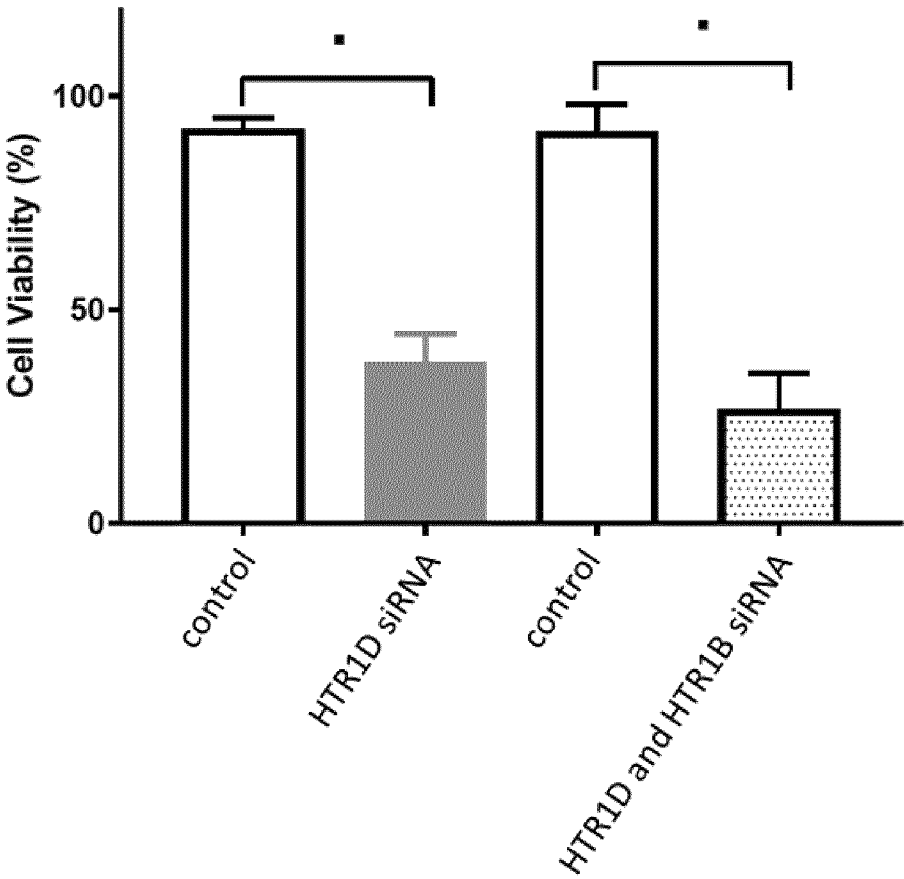


FIG. 32

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2020/056957

| A. CLASSIFICATION OF SUBJECT MATTER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| INV.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | A61K31/495<br>A61K35/00                                                                                                                                                                                                                                                                                                                                                                        | A61K31/496<br>G01N33/574                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | A61K45/06                                                                                                                                                                                                                                                                                                                                                                                      | A61K39/00                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                | A61K47/54                                                            |
| ADD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| B. FIELDS SEARCHED                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| Minimum documentation searched (classification system followed by classification symbols)<br>A61K G01N                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                             | Relevant to claim No.                                                |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <p>NILGUN GURBUZ ET AL: "Down-Regulation of 5-HT1B and 5-HT1D Receptors Inhibits Proliferation, Clonogenicity and Invasion of Human Pancreatic Cancer Cells", PLOS ONE, vol. 9, no. 8, 29 August 2014 (2014-08-29), page e105245, XP055697474, DOI: 10.1371/journal.pone.0105245 title, abstract, Fig. 2, 3, 6; paragr. bridging p. 9/10</p> <p style="text-align: center;">-----<br/>-/--</p> | 1-14                                                                 |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p> |                                                                                                                                                                                                                                                                                                                                                                                                |                                                                      |
| Date of the actual completion of the international search<br><br>27 May 2020                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                | Date of mailing of the international search report<br><br>29/07/2020 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                | Authorized officer<br><br>Dahse, Thomas                              |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2020/056957

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                       |
|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                              | Relevant to claim No. |
| A                                                    | <p>JIELU PAN ET AL: "Extracts of Zuo Jin Wan, a traditional Chinese medicine, phenocopies 5-HTR1D antagonist in attenuating Wnt/[beta]-catenin signaling in colorectal cancer cells", BMC COMPLEMENTARY AND ALTERNATIVE MEDICINE, BIOMED CENTRAL LTD, LONDON, UK, vol. 17, no. 1, 28 November 2017 (2017-11-28), pages 1-11, XP021251131, DOI: 10.1186/S12906-017-2006-7 title, abstract; p. 10, last of col.1 and conclusions</p> <p>-----</p> | 1-14                  |
| A                                                    | <p>WO 98/31669 A1 (PF MEDICAMENT [FR]; HALAZY SERGE [FR] ET AL.)<br/>23 July 1998 (1998-07-23)<br/>claim 17, p. 47, last to p. 48, first</p> <p>-----</p>                                                                                                                                                                                                                                                                                       | 1-14                  |
| A                                                    | <p>EP 0 795 328 A1 (PFIZER [US])<br/>17 September 1997 (1997-09-17)<br/>p. 1, first paragr.; claims</p> <p>-----</p>                                                                                                                                                                                                                                                                                                                            | 1-14                  |
| A                                                    | <p>PAI VAIBHAV P ET AL: "Altered serotonin physiology in human breast cancers favors paradoxical growth and cell survival", BREAST CANCER RESEARCH, CURRENT MEDICINE GROUP LTD, GB, vol. 11, no. 6, 10 November 2009 (2009-11-10), page R81, XP021065292, ISSN: 1465-5411, DOI: 10.1186/BCR2448 Fig. 6(a); title, abstract; p. 4, col. 2, second paragr.</p> <p>-----</p>                                                                       | 1-14                  |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2020/056957

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

13(completely); 1-12, 14(partially)

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 13(completely); 1-12, 14(partially)

directed to compounds/compositions comprising a 5HTR-1D inhibitor for use in the prevention/treatment of cancer in a subject in need thereof, wherein the cancer is selected from breast cancer, liver cancer, mesothelioma, head and neck squamous cell carcinoma, kidney cancer, gastric cancer and cervix cancer.

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2. claims: 1-12, 14(all partially)

directed to compounds/compositions comprising a 5HTR-1D inhibitor for use in the prevention/treatment of cancer in a subject in need thereof, wherein the cancer is selected from lung cancer, brain cancer

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3. claims: 1-8, 11, 12, 14(all partially)

directed to compounds/compositions comprising a 5HTR-1D inhibitor for use in the prevention/treatment of cancer in a subject in need thereof, wherein the cancer is any further cancer mentioned in the application and not being covered by inventions I and II.

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4. claim: 15

directed to an in vitro cancer diagnosis, stratification and/or prognosis method as defined in claim 15.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/056957

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date     |
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|                                           |                     | FR 2758327 A1 17-07-1998   |                         |
|                                           |                     | WO 9831669 A1 23-07-1998   |                         |
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|                                           |                     | EP 0795328 A1 17-09-1997   |                         |
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