

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 December 2008 (18.12.2008)

PCT

(10) International Publication Number
WO 2008/153573 A1

(51) International Patent Classification:

C07D 295/145 (2006.01) **A61P 25/00** (2006.01)
C07D 401/12 (2006.01)

(21) International Application Number:

PCT/US2007/071412

(22) International Filing Date: 15 June 2007 (15.06.2007)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

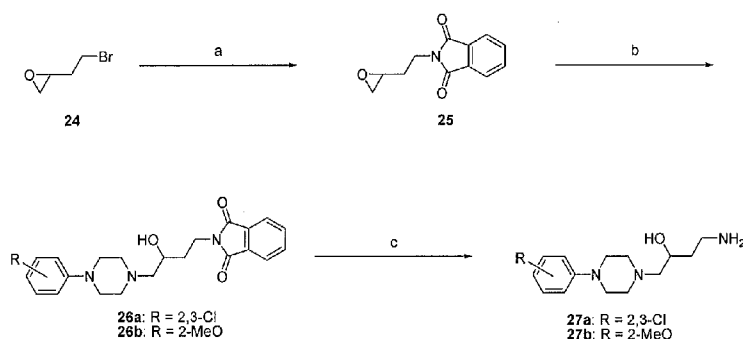
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: 4-PHENYLPYPERAZINE DERIVATIVES WITH FUNCTIONALIZED LINKERS AS DOPAMINE D₃ RECEPTOR SELECTIVE LIGANDS AND METHODS OF USE

Synthesis of the 3-hydroxyl amines **27^a**

Figure 1



^a Reagents and conditions: (a) phthalimid potassium salt, DMF, microwave, 100 °C, 20 min; (b) 1-(2,3-dichlorophenyl)- or 1-(2-methoxyphenyl)-piperazine, 2-PrOH, microwave, 90 °C, 20 min; (c) hydrazine, ethanol, microwave, 90 °C, 20 min.

(57) Abstract: Dopamine D₃ receptor antagonists and partial agonists are known to modulate the reinforcing and drug-seeking effects induced by cocaine and other abused substances. By introducing functionality into the butylamide linking chain of the 4-phenylpiperazine class of ligands, improved D₃ receptor affinity and selectivity, as well as water solubility, is achieved. A series of linking-chain derivatives are disclosed wherein functionality such as OH or OAc groups have been introduced into the linking chain. In general, these modifications are well tolerated at D₃ receptors and achieve high selectivity over D₂ and D₄ receptors.



FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

4-Phenylpiperazine Derivatives with functionalized linkers as Dopamine D₃ Receptor Selective Ligands and Methods of Use

BACKGROUND

The dopamine receptor system plays a key role in numerous neuropsychiatric and neurological disorders and investigation into mechanistic underpinnings and neuroadaptations within this family of receptors has been the focus of intensive research over the past decade. The dopamine D₃ receptor subtype has been hypothesized to play a fundamental role, for example, in the abuse-related effects of cocaine and other drugs of abuse. Hence, there is a well recognized need to develop novel, selective and bioavailable dopamine D₃ receptor ligands.

Further reasons for pursuing dopamine D₃ receptor selective ligands as medications for various conditions come from the brain localization of D₃ receptors, which are primarily expressed in limbic regions of the brain, including the nucleus accumbens. D₃ receptor blockade may attenuate drug reward and/or reinforcement while avoiding the risk of extrapyramidal side effects associated with the blockade of the more ubiquitous D₂ receptors.

The high degree of amino acid homology within the binding sites of the dopamine D₂-like receptors, and especially between the D₂ and D₃ dopamine receptor subtypes, has provided a formidable challenge in the pursuit to discover dopamine D₃-selective compounds. Thus far, high dopamine D₂/D₃ selectivity has generally been achieved with relatively large molecules, characterized, for example, by a heterocyclic moiety bridged by an unsubstituted 4-carbon chain or carbocycle to an extended or substituted arylamide or a corresponding bioisotere.

In addition to optimizing pharmacological selectivity, it is also important that dopamine D₃-selective compounds be able to penetrate the blood brain barrier (BBB) and have appropriate pharmacokinetics to facilitate interpretation of *in vivo* results. However, generally relatively high doses of D₃-selective agents have been required for behavioral activity. It is not known whether these required high doses are due to a low permeability surface area product of these agents for crossing the BBB, high peripheral metabolism, large uptake in some other organ or compartment, or is due to some other reason.

Therefore, there is a well recognized need in the art for highly D₃-selective compounds that are able to penetrate the blood brain barrier, and that show activity at relatively low dosages.

BRIEF DESCRIPTION OF THE DRAWINGS

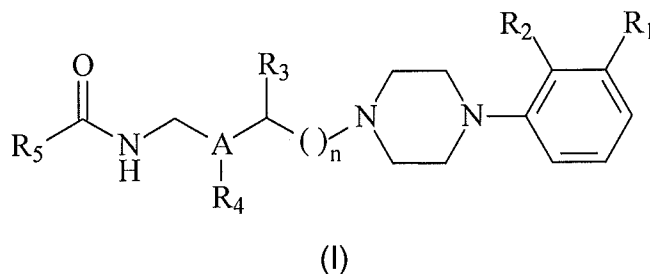
Figure 1: Synthesis of the 3-hydroxyl amines **27**.

Figure 2: Synthesis of the 2-hydroxyl amines **30**.

Figure 3: Synthesis of Compounds **2-23**.

DESCRIPTION OF THE INVENTION

The present invention relates to chemical compounds of the following chemical formula:



Wherein:

A = trans CH=CH or C;

n = 0 or 1;

R₁ and R₂ = independently represent hydrogen, halogen, or alkoxy;

R₃ or R₄ = H, OH, OAc, alkoxy, halogen, amino, nitro, alkoxy, alkyl, acyl and pyridyl;

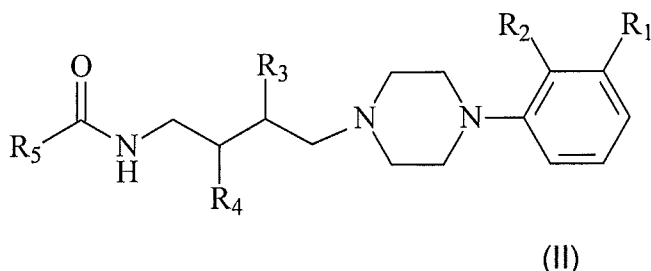
R₅ = phenyl, indole, thiophene, benzofuran, fluorenyl, or 2-pyridylphenyl; and R₅ is optionally substituted with one or more of hydrogen, halogen, amino, nitro, hydroxyl, alkoxy, alkyl, acyl and pyridyl, substitution may occur at any of the ortho, meta, or para positions;

including all enantiomers and pharmaceutical salts.

In particular, when R₃ and R₄ are not H, chiral centers are present on the butyl amide linking chain and are included within the scope of the invention.

In one embodiment of the invention A in Formula (I) is C.

In one embodiment, the present invention is directed to compounds of the following chemical formula:



Wherein

R₁ and R₂ = 2-methoxy or 2,3-dichloro;

R₃ or R₄ = OH, OAc, H; and

R₅ = indole, thiophene, benzofuran, fluorenyl, or 2-pyridylphenyl, and R₅ is substituted with one or more of methoxy, fluoro, or iodo;
including all enantiomers and pharmaceutical salts.

Dopamine D₃ receptor antagonists and partial agonists are known to modulate the reinforcing and drug-seeking effects induced by cocaine and other abused substances. The introduction of functionality into the butylamide linking chain of the 4-phenylpiperazine class of ligands, improves D₃ receptor affinity and selectivity, as well as water solubility. See *J. Med. Chem.* 2005, 48, 839-848. Along these lines, a series of linking-chain derivatives wherein functionality such as OH, OAc, etc., are introduced into the linking chain is disclosed.

In general, these modifications are well tolerated at D₃ receptors (K_i < 1-5 nM) and several analogues demonstrated >100-fold selectivity over D₂ and D₄ receptors using competition binding assays in HEK 293 cells transfected with either hD_{2L}, hD₃ or hD₄ dopamine receptors. Furthermore, addition of these groups affected efficacy of the compounds as measured by quinpirole stimulation of mitogenesis at human dopamine D₃ receptors transfected into Chinese hamster ovary (CHO) cells. These compounds also provide additional tools with which to elucidate the role of D₃ receptors in drug reinforcement in vivo.

The dopamine D₃ receptor subtype is a member of the dopamine D₂ family of receptors. These receptors are involved in a number of CNS disorders including but not limited to psychostimulant abuse, psychosis and Parkinson's disease. (Newman, A. H.; Grundt, P.; Nader, M. A., *Dopamine D3 receptor partial agonists and*

antagonists as potential drug abuse therapeutic agents. J. Med. Chem. **2005**, 48, 3663-3679.; Heidbreder, C. A.; Andreoli, M.; Marcon, C.; Thanos, P. K.; Ashby, C. R.; Gardner, E. L., *Role of dopamine D-3 receptors in the addictive properties of ethanol*. Drugs Today **2004**, 40, 355-365.; Joyce, J. N.; Millan, M. J., *Dopamine D-3 receptor antagonists as therapeutic agents*. Drug Discov. Today **2005**, 10, 917-925; See also, Le Foll, B.; Goldberg, S. R.; Sokoloff, P., *The dopamine D-3 receptor and drug dependence: Effects on reward or beyond?* Neuropharmacology 2005, 49, 525-541; Luedtke, R. R.; Mach, R. H., *Progress in developing D3 dopamine receptor ligands as potential therapeutic agents for neurological and neuropsychiatric disorders* Curr. Pharm. Design 2003, 9, 643-671; Boeckler, F.; Gmeiner, P., *The structural evolution of dopamine D-3 receptor ligands: Structure-activity relationships and selected neuropharmacological aspects* Pharmacol. Ther. 2006, 112, 281-333.)

Compounds that bind with high affinity and selectivity to D₃ receptors not only provide important tools with which to study the structure and function of this receptor subtype, but also have a therapeutic effect in the treatment of numerous psychiatric and neurologic disorders.

It is known in the art that the D₂ family of receptors (which includes D₃) are increased in cocaine addicts and monkeys trained to self administer cocaine. See Volkow, N. D.; Wang, G. J.; Fowler, J. S.; Logan, J.; Gatley, S. J.; Wong, C.; Hitzemann, R.; Pappas, N. R., *Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D-2 receptors*, J. Pharmacol. Exp. Ther. 1999, 291, 409-415; Volkow, N. D.; Fowler, J. S.; Wang, G. J.; Swanson, J. M., *Dopamine in drug abuse and addiction: results from imaging studies and treatment implications*, Mol. Psychiatry 2004, 9, 557-569; Nader, M. A.; Morgan, D.; Gage, H. D.; Nader, S. H.; Calhoun, T. L.; Buchheimer, N.; Ehrenkaufer, R.; Mach, R. H., *PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys*, Nat. Neurosci. 2006, 9, 1050-1056.

The 4-phenylpiperazine derivatives are an important class of dopamine D₃ selective ligands. However, due to their highly lipophilic nature, these compounds often suffer from solubility problems in aqueous media and reduced bioavailability. To address these problems, functionality (e.g. OH, OCH₃, OAc, etc.) is introduced into the carbon chain linker of these compounds. Compared to currently available

dopamine D₃ receptor ligands, the resulting compounds show improved pharmacological properties and D₃ selectivities, but due to their more hydrophilic nature these derivatives also have improved water solubility and bioavailability.

The more hydrophilic nature of these derivatives is shown by the cLogP (calculated measure of lipophilicity) and polar surface areas (PSA). See Table 1. As expected, the introduction of a hydroxyl group into the butyl linking chain resulted in lower clogP values, showing decreased lipophilicity, compared to the corresponding parent olefinic or aliphatic compounds. The calculated polar surface area (PSA) was significantly increased (by 20 Å²). Values less than 75 Å² are considered as being favorable for brain penetration. See Grundt, P.; Prevatt, K. M.; Cao, J.; Taylor, J.; Floresca, C. Z.; Choi, J.-K.; Jenkins, B. G.; Luedtke, R. R.; Newman A. H. *Heterocyclic Analogues of N-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-butyl)-aryl-carboxamides with Functionalized Linking Chains as Novel Dopamine D₃ Receptor Ligands: Potential Substance Abuse Therapeutic Agents*. J. Med. Chem. **2007**, in press.

According to Lipinski's "rule of 5" cLogP values in the 2-5 range are expected to have drug like properties. See Lipinski, C. A., *Drug-like properties and the causes of poor solubility and poor permeability*, J. Pharmacol. Toxicol. Methods 2000, 44, 235-249. Comparisons of the hydroxylated analogues with their saturated butyl or olefinic counterparts demonstrate that both PSA and particularly cLogP values are predictive of improved "drug-like", soluble, bioavailable and CNS penetrant profiles. The PSA values were calculated according to Ertl, P.; Rohde, B.; Selzer, P., *Fast, Calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties*, 2000, 43, 3714-3717. CLogP values were calculated using *Cambridgesoft ChemDraw Ultra 9.0*, 2004.

Based on their neurochemical and behavioral properties, the dopamine D₃ receptor selective ligands of the present invention are useful in methods for the treatment of all addictions, especially including nicotine and alcohol, and psychostimulant abuse, such as of cocaine, amphetamine, and derivatives thereof. The dopamine D₃ receptor selective ligands of the present invention are also useful in the treatment of schizophrenia and Parkinson's disease and dyskinesias

associated with these disorders and treatment thereof. Generally the methods involve administering a pharmaceutically effective amount of a compound of the present invention to a patient in need thereof.

D₃ selectivity is expressed as D₂/D₃; a ratio that is derived from the K_i value at D₂ over the K_i value at D₃ receptors. Hence, a compound that exhibits higher affinity at D₃ than at D₂ receptors, has a D₂/D₃ ratio >1." See Newman, A. H.; Grundt, P.; Nader, M. A., *Dopamine D3 receptor partial agonists and antagonists as potential drug abuse therapeutic agents. J. Med. Chem.* 2005, 48, 3663-3679.

The term "pharmaceutically effective amount" as used herein means an amount of the compound that produces any therapeutic effect or imaging effect in a patient. Therapeutic effect in a patient preferably relates to one of the above-mentioned conditions.

The term "alkyl" is used herein to refer to a branched or unbranched, saturated or unsaturated, monovalent hydrocarbon radical having from 1-8 carbons, including arylalkyls. Suitable alkyl radicals include, for example, methyl, ethyl, n-propyl, i-propyl, 2-propenyl (or allyl), n-butyl, t-butyl, i-butyl (or 2-methylpropyl), i-amyl, n-amyl, hexyl, etc. As used herein, the term alkyl encompasses "substituted alkyls." The term "substituted alkyl" refers to alkyl as just described including one or more functional groups such as lower alkyl, aryl, aralkyl, acyl, halogen (i.e., alkylhalos, e.g., CF₃), hydroxyl, amino, acylamino, acyloxy, alkoxy, mercapto and the like. These groups may be attached to any carbon atom of the lower alkyl moiety.

The term "alkoxy" is used herein to refer to the --OR group, where R is a lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl. Suitable alkoxy radicals include, for example, methoxy, ethoxy, phenoxy, t-butoxy, etc.

The term "lower alkyl" means C₁ to C₃. The term "halogen" is used herein to refer to fluorine, bromine, chlorine, and iodine atoms. The term "hydroxyl" is used herein to refer to the group --OH.

As used herein, "psychostimulant abuse" has its conventional meaning, i.e., misuse or addiction of a psychostimulant, such as cocaine, amphetamine and derivatives thereof. Typically, cocaine is taken by a person due to a craving for cocaine generated by its prior use. Cocaine is abused when it is used for

gratification, producing effects not required or recommended for therapy. The resultant high use of cocaine produces many serious and adverse side effects. As such, it is highly desirable to reduce the number and/or intensity of episodes in which a person experiences a craving for the substance or, more preferably, to eliminate the craving episodes entirely. Dopamine D₃ antagonists or partial agonists have demonstrated utility in reducing craving in animal models (Pilla, M. et al. *Nature* 400:371-375 (1999), Vorel, S. R. et al. *J. Neurosci.* 22:9595-9603 (2002), DiCiano, P. et al. *Neuropsychopharmacology* 28:329-338 (2003)).

"Treatment" or "treating," as used herein, refers to any administration of a compound of the present invention and includes: (i) inhibiting the symptoms of the disease, e.g., cocaine addiction; and/or (ii) lessening or inhibiting the long term effects of the disease, e.g., cocaine addiction. In therapeutic applications, compositions are administered to a patient already suffering from the disease, e.g., cocaine addiction or Parkinson's disease, in a pharmaceutically effective amount.

In conjunction with the foregoing method, the present invention provides pharmaceutical compositions comprising a compound disclosed herein and a pharmaceutically acceptable diluent, carrier or excipient. While it is possible to administer the active ingredient of this invention alone, it is preferable to present it as part of a pharmaceutical formulation. The formulations of the present invention comprise at least one compound described herein in a therapeutically or pharmaceutically effective dose together with a pharmacologically or therapeutically acceptable carrier. The phrase "pharmaceutically or therapeutically acceptable carrier," as used herein, refers to a carrier medium which does not interfere with the effectiveness of the biological activity of the active ingredients, especially D₃ receptor binding of a compound of the present invention, and which is not toxic to the host or patient.

The pharmaceutical compositions of the present invention can be in a variety of forms. These include, for example, solid, semi-solid and liquid dosage forms, such as tablets, pills, powders, liquid solutions or suspensions, liposomes, injectable and infusible solutions. Inhalable preparations, such as aerosols, are also included. Preferred formulations are those directed to oral, intranasal and parenteral applications, but it will be appreciated that the preferred form will depend on the

particular therapeutic application at hand. The methods for the formulation and preparation of therapeutic compositions comprising the compounds of the invention are well known in the art and are described in, for example, REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985)), THE MERCK INDEX 11th Ed., (Merck & Co. 1989), and Langer, Science 249: 1527-1533 (1990), the teachings of which are incorporated herein by reference.

For parenteral administration, for example, the pharmaceutical compositions comprise a solution of a compound of the present invention, as described above, dissolved or suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used including, for example, water, buffered water, 0.4% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well-known sterilization techniques, or they may be sterile filtered. The resulting aqueous solutions may be packaged for use as is or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions including pH adjusting and buffering agents, wetting agents and the like, such as, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

For solid compositions, conventional nontoxic solid carriers may be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally about 1% to 95%, preferably 10% to about 95% of the active ingredient and, more preferably, about 25% to about 75% of the active ingredient.

For aerosol administration, the compounds of the present invention are preferably supplied in a finely divided form along with a surfactant and propellant. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids

containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. A carrier can also be included as desired, as with, e.g., lecithin, for intranasal delivery.

Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved condition is retained. When the symptoms have been alleviated to the desired level, treatment can cease. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of the disease symptoms.

In general, a suitable effective dose of the compounds of the present invention will be in the range of 0.05 to 1000 milligram (mg) per recipient per day, preferably in the range of 0.1 to 100 mg per day. The desired dosage is preferably presented in one, two, three, four or more subdoses administered at appropriate intervals throughout the day. These subdoses can be administered as unit dosage forms, for example, containing 0.01 to 1000 mg, preferably 0.01 to 100 mg of active ingredient per unit dosage form. Again, the desired dosage will depend on, for example, the particular compound employed, the disease to be treated, the manner of administration, the weight and general state of health of the patient, and the judgment of the prescribing physician.

Based on their neurochemical and behavioral properties, the D₃ receptor selective ligands of the present invention are also useful as imaging probes. The present compounds may be useful for functional MRI imaging of D₃ receptors. In addition, the dopamine D₃ receptor selective ligands of the present invention are useful as imaging agents for dopamine D₃ receptors and as imaging probes for neurodegenerative disorders (e.g., Parkinson's disease). As such, in another aspect, the present invention provides a method of selectively imaging dopamine binding sites of the central nervous system of a subject, such as the brain of a human patient, the method comprising:

(a) administering to a human in need thereof an inventive compound of the present invention; and

(b) detecting the binding of the compound to the central nervous system tissue, such as the dopamine D₃ receptors in the brain.

Moreover, in yet another aspect, the present invention provides a method for detecting or monitoring a disease resulting from abnormal distribution and/or density of dopamine D₃ receptor in the central nervous system of a subject, comprising:

(a) administering to the subject a detectably labeled compound of the invention;

(b) detecting the binding of that compound to dopamine D₃ receptor in the central nervous system;

(c) determining the distribution and/or density of the dopamine D₃ receptor in the central nervous system tissue;

(d) comparing the distribution and/or density obtained in (c) with the distribution and/or density of dopamine D₃ receptor in a corresponding normal tissue; and

(e) diagnosing a disease state by a difference in the distribution and/or density between the normal tissue and the subject tissue.

In a presently preferred embodiment, the dopamine selective ligands of the present invention are labeled with a radioactive label using standard labeling techniques known to and used by those of skill in the art. Suitable labels include, but are not limited to: ¹²³I, ¹¹C, ¹⁸F, or ⁹⁹Tc. In addition, binding of the dopamine D₃ receptor selective ligands to the brain, such as limbic brain regions, including the Nucleus Accumbens and islands of Calleja, is detected using methods known in the art, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), or magnetic resonance imaging (MRI). (See, e.g., Yokoi F. et al., *Neuropsychopharmacology* 27(2):248-59(2002); Pilowsky L. S., *Nucl Med Commun* 22(7):829-33(2001); Soares JC and Innis RB, *Biol Psychiatry* 46(5):600-15(1999); and Videbaek C, *J Cereb Blood Flow Metab* 21(1):92-7(2001), the teachings of which are incorporated herein by reference.

Preferably SPECT imaging employs gamma-emitting derivatives of the ligands described herein (e.g., dopamine D₃ receptor selective ligands labeled with ¹²³I or ⁹⁹Tc). Yokoi et al. (supra) have mapped the normal distribution of dopamine D₂ and D₃ receptors in humans. Using this method, one can diagnose and/or monitor

neurodegenerative disorders, such as Parkinson's disease, characterized by the progressive degeneration of dopamergic nerve terminals.

EXAMPLES

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 instrument. Proton chemical shifts are reported as parts per million (δ ppm) relative to tetramethylsilane (0.00 ppm) as an internal standard. Coupling constants are measured in hertz (Hz). Chemical shifts for ^{13}C NMR spectra are reported as δ relative to the deuterium signal of the solvent (CDCl_3 , 77.5 ppm, CD_3OD 49.3). Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within 0.4% of calculated values. If not stated otherwise all final compounds were purified by column chromatography (silica gel, Merck, 230-400 mesh, 60 Å) or thin layer chromatography (silica gel, Analtech, 1000 micron) using $\text{EtOAc}/\text{CHCl}_3/\text{MeOH}$ 5:5:1, 1% triethylamine or $\text{CHCl}_3/\text{MeOH}$ 10:1, 1% triethylamine as an eluent. Microwave reactions were performed in a CEM Discover Labmate system equipped with a 80 mL pressure vessel. Yields and reaction conditions are not optimized. Generally, yields and spectroscopic data refer to the free base.

Methods for performing in vitro dopamine receptor binding studies are described in Huang et al. *J. Med. Chem.* 44:1815-1826 (2001) and Luedtke et al. *Synapse* 38:438-439 (2000), the contents of which are hereby incorporated by reference. These papers describe radioactively labeled dopamine receptor selective ligands binding with picomolar affinity and nonselectivity to D_2 and D_3 dopamine receptors expressed in Sf9 and HEK 293 cells. ^{125}I -IABN binds with 7- to 10-fold lower affinity to human $\text{D}_{4.4}$ dopamine receptors expressed in HEK 293 cells. Dissociation constants (K_d) calculated from kinetic experiments were found to be in agreement with equilibrium K_d values obtained from saturation binding studies. Saturation plots of the binding of ^{125}I -IABN with rat caudate membrane preparations were monophasic and exhibited low nonspecific binding. The pharmacologic profile of the binding of ^{125}I -IABN to rat caudate was found to be consistent with a D_2 -like receptor, suggesting that in the caudate the ligand binds primarily to D_2 dopamine receptors. IABN was found to bind with low affinity to σ_1 and σ_2 binding sites, as well as to D_{1a} dopamine receptors. Quantitative autoradiographic studies using rat brain

indicated that ^{125}I -IABN selectively labels the striatum and the olfactory tubercle area, which is consistent with the labeling receptors expressed in HEK cells. Therefore, ^{125}I -IABN appears to be a high affinity, selective antagonist at D_2 -like dopamine receptors.

Human dopamine D_2 -long (D_2) and D_3 (D_3) receptors were expressed in HEK cells. In brief, stably transfected HEK cells expressing the human D_2 -long and the D_3 dopamine receptor were developed using the pIRES bicistronic expression vector (CLONTECH; Palo Alto, Calif.). The level of expression of D_2 or D_3 receptors was determined to be greater than 2,000 fmoles/mg protein. For comparison, human dopamine D_4 (D_4) receptors were obtained from HEK 293 cells stably transfected with a PCR product of a human cDNA coding for the D4.4 form of the human D_4 dopamine receptor. The density of binding sites is approximately 1000 fmol/mg protein.

To measure D_2 and D_3 stimulation of mitogenesis (agonist assay) or D_2 and D_3 inhibition of quinpirole stimulation of mitogenesis (antagonist assay), CHOp-cells (human receptor) were seeded in a 96-well plate at a concentration of 5,000 cells/well. The cells were incubated at 37° C. in α -MEM with 10% FBS, 0.05% penicillin-streptomycin, and 200 $\mu\text{g}/\text{mL}$ of G418. After 48 hours, the cells were rinsed twice with serum-free α -MEM and incubated for 24 hours at 37° C. In the functional assay for agonism, the medium was removed and replaced with 90 μl of serum-free α -MEM and 10 μl of test compound in sterile water; in the antagonist assay, the test compound was diluted in sterile water plus 30 nM quinpirole. After another 24-hour incubation at 37° C., 0.25 μCi of [^3H]thymidine was added to each well and the plates were further incubated for 2 hours at 37° C. The cells were then trypsinized, and the plates were filtered and counted as usual in the art. Quinpirole was run on every plate as an internal standard.

The procedures to determine the binding affinities at the human dopamine D_2 -like receptors, the binding affinities at the serotonin $5\text{HT}_{1\text{A}}$, $5\text{HT}_{2\text{A}}$ and $5\text{HT}_{2\text{C}}$ receptors and functional mitogenesis assay are known in the art. See *J. Med. Chem.* **2005**, 48, 839-848. See also, *NIDA Research Monograph # 178, Proceedings of the College of Drug Dependence*, p. 440-466, **1998**. Both of these references are incorporated by reference.

The racemic hydroxybutyl amine intermediates needed to prepare the 3-hydroxy derivatives **16-19** and 2-hydroxy analogues **21-23** were synthesized as depicted in Figures 1 and 2. In both cases, the synthetic routes used bifunctional 2-(2-bromoethyl)oxirane as starting material. See Cruickshank, P. A.; Fishman, M., "Studies In Alkylation.2. Reactions Of Epoxyalkyl Bromides", *J. Org. Chem.* **1969**, 34, 4060-4065, incorporated by reference. All key steps were found to be regioselective and only the products depicted were isolated. The amines (Figure 1) were synthesized via a modified Gabriel synthesis. No side products were observed in the alkylation reaction to form the phthalimide.

The opening of the oxirane moiety occurred selectively at the least substituted side to yield the 3-hydroxy phthalimides, which were then deprotected with hydrazine to afford the hydroxylamines. In the case of the 2-hydroxy amines (30, Figure 2) the butylpiperazine bond was formed first, followed by a regioselective opening of the epoxide with sodium azide and a Schlesinger-type reduction. The general reaction sequence used to prepare the dopamine D₃ receptor preferring analogues **2-23** incorporating a butyl, butenyl or hydroxybutyl linking chain as depicted in Figure 3. The required carboxylic acids were prepared according to procedures known in the art. See *J. Med. Chem.* **2001**, 44, 3175-3186. See also, *Synlett* **2000**, 829-831. Both of these references are incorporated by reference.

The general synthesis of the butyl amines and the butenyl amines is also known in the art. See *J. Med. Chem.* **2005**, 48, 839-848; *J. Med. Chem.* **2001**, *J. Med. Chem.* **2003**, 46, 3883-3899; and *Bioorg. Med. Chem. Lett.* **2003**, 13, 2179-2183. All of these references are incorporated by reference.

General procedure for the synthesis of carboxylic acid amides. The 1-imidazole adduct appropriate carboxylic acid was reacted with the suitable secondary amine derivative as known in the art. See *J. Med. Chem.* **2005**, 48, 839-848, incorporated by reference. The crude product was purified by chromatography, structurally characterized and then converted into its oxalate or hydrochloride for biological evaluation.

Example 1

***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-9*H*-fluorene-2-carboxamide (7).** Prepared from 9*H*-fluorene-2-carboxylic acid and 4-(4-(2-

methoxyphenyl)-piperazin-1-yl)-butylamine according to the general procedure. Yield: 74 %. Mp. (hydrochloride): 208-210°C. ¹H NMR (CDCl₃): δ 1.67-1.73 (m, 4H), 2.47 (t, *J* 6.7, 2H), 2.65 (s, 4H), 3.04 (s, 4H), 3.51 (q, *J* 6.1, 2H), 3.84 (s, 3H), 3.91 (s, 2H), 6.82-6.88 (m, 4H), 6.98 (dt, *J* 7.8, 4.6, 1H), 7.35 (td, *J* 7.4, 1.2, 1H), 7.40 (t, *J* 7.0, 1H), 7.55 (d, *J* 7.0, 1H), 7.75-7.77 (m, 2H), 7.81 (d, *J* 8.0, 1H), 7.96 (s, 1H). ¹³C NMR (CDCl₃): δ 25.0, 27.9, 37.3, 40.5, 50.93, 53.9, 55.8, 58.5, 111.5, 118.6, 120.1, 121.0, 121.4, 123.4, 124.4, 125.6, 126.3, 127.4, 128.0, 133.8, 141.2, 141.6, 143.8, 144.4, 145.1, 152.7, 168.6. Anal. (C₂₉H₃₃N₃O₂·2HCl·0.5H₂O) C, H, N.

Example 2

***N*-(4-(4-(2-Methoxy-phenyl)-piperazin-1-yl)-butyl)-4-pyridin-2-yl-benzamide (8).** Prepared from 4-pyridin-2-yl-benzoic acid hydrochloride and 4-(4-(2-methoxy-phenyl)-piperazin-1-yl)-butylamine according to the general procedure. Yield: 53%. Mp. (oxalate): foam. ¹H NMR (CDCl₃): δ 1.67-1.74 (m, 4H), 2.49 (t, *J* 6.84, 2H), 2.67 (s, 2H), 3.07 (s, 2H), 3.51 (q, *J* 6.0, 2H), 3.84 (s, 3H), 6.83 (m, 5H), 7.26 (m, 1H), 7.73-7.79 (m, 2H), 7.89 (d, *J* 8.2, 2H), 8.06 (d, *J* 8.6, 2H), 8.71 (dt, *J* 4.7, 1.3, 1H). ¹³C NMR (CDCl₃): δ 24.8, 27.9, 40.4, 50.8, 53.9, 55.8, 58.5, 111.6, 118.7, 121.3, 121.4, 123.1, 123.4, 127.4, 127.9, 135.6, 137.3, 142.5, 150.3, 152.7, 156.7, 167.8. Anal. (C₂₇H₃₂N₄O₂·(COOH)₂·0.75H₂O) C, H, N.

Example 3

***N*-(4-(4-(2,3-Dichloro-phenyl)-piperazin-1-yl)-*trans*-but-2-enyl)-4-(6-oxo-1,6-dihydro-pyridin-2-yl)-benzamide (9).** A suspension of 0.12 g (0.53 mmol) 4-(6-oxo-1,6-dihydro-pyridin-2-yl)-benzoic acid, 0.13 g (0.64 mmol) dicyclohexylcarbodiimide, 0.1 g (0.7 mmol) 1-hydroxybenzotriazole hydrate in 15 mL DMF was treated at 0°C with 0.16 g (0.53 mmol) 4-(4-(2,3-chloro-phenyl)-piperazin-1-yl)-*trans*-but-2-enyl amine and 0.17 mL (1.2 mmol) triethylamine. The reaction mixture was stirred at room temperature for 3 days and filtered. The solvent was removed *in vacuo* and the residue was taken up in saturated sodium bicarbonate and CHCl₃. The combined organics were dried with sodium sulphate, concentrated and the crude product was purified by thin layer chromatography. Yield: 0.10 g (38%). Mp. (oxalate): 153-154°C. ¹H NMR (CDCl₃): δ 2.67 (s, 4 H), 3.06 (s, 6 H), 4.11 (m, 2H), 5.74-5.83 (m, 2H), 6.51-6.54 (m, 2H), 6.70 (t, *J* 5.3, 1 H), 6.95 (dd, *J* 6.7, 2.9, 1H), 7.11-7.17 (m, 2H), 7.50 (dd, *J* 9.1, 7.0, 1H), 7.72 (d, *J* 8.3, 2 H), 7.85

(d, J 8.4, 2 H). ^{13}C NMR (CDCl_3): δ 40.6, 50.2, 52.3, 59.4, 105.9, 17.9, 118.1, 124.1, 126.3, 126.6, 126.7, 127.0, 127.3, 130.2, 133.2, 135.0, 135.7, 141.6, 145.6, 150.4, 164.5, 167.0. Anal. ($\text{C}_{26}\text{H}_{26}\text{Cl}_2\text{N}_4\text{O}_2 \cdot 1.5 (\text{COOH})_2$) C, H, N.

Example 4

***N*-(4-(4-(2,3-Dichloro-phenyl)-piperazin-1-yl)-*trans*-but-2-enyl)-4-(6-methyl-pyridin-2-yl)-benzamide (10).** Prepared from 4-(6-methylpyridin-2-yl)benzoic acid hydrochloride and 4-(4-(2,3-chloro-phenyl)-piperazin-1-yl)-*trans*-but-2-enyl amine according to the general procedure. Yield: 18%. Mp. (oxalate): 125-126 °C. ^1H NMR (CDCl_3): δ 2.63 (s, 7H), 3.08 (s, 6H), 4.12 (m, 2H), 5.78-5.80 (m, 2H), 6.42 (s, br, 1H), 6.95 (d, J 6.7, 2.7, 1H), 7.11-7.16 (m, 3H), 7.55 (d, J 7.7, 1H), 7.65 (t, J 7.6, 1H), 7.87 (d, J 8.7, 2H), 8.05 (d, J 8.3, 2H). ^{13}C NMR (CDCl_3): δ 25.2, 42.0, 51.7, 53.7, 60.7, 118.3, 119.1, 122.8, 125.0, 127.5, 127.8, 127.9, 129.4, 130.2, 134.4, 134.7, 137.5, 143.1, 151.7, 156.0, 159.0, 167.4. Anal. ($\text{C}_{27}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O} \cdot 2(\text{COOH})_2$): C, H, N.

Example 5

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-*trans*-but-2-enyl)-4-(3-methyl-pyridin-2-yl)-benzamide (11).** Prepared from 4-(3-methylpyridin-2-yl)benzoic acid hydrochloride and 4-(4-(2,3-chloro-phenyl)-piperazin-1-yl)-*trans*-but-2-enyl amine according to the general procedure. Yield: 55 %. Mp. (oxalate): foam. ^1H NMR (CDCl_3): δ 2.34 (s, 3H), 2.65 (s, 4H), 3.07-3.10 (m, 6H), 6.12 (m, 2H), 5.78-5.82 (m, 2H), 6.49 (t, J 5.5, 1H), 6.95 (dd, J 6.5, 2.9, 1H), 7.12-7.16 (m, 2H), 7.21 (dd, J 7.6, 4.8, 1H), 7.57-7.62 (m, 3H), 7.86 (dt, J 8.6, 2.0, 2H), 8.53 (dt, J 4.2, 0.8, 1H). ^{13}C NMR (CDCl_3): δ 20.4, 42.0, 51.7, 53.7, 60.7, 119.1, 123.0, 125.0, 127.3, 127.9, 129.4, 129.7, 130.3, 131.4, 134.2, 134.4, 139.2, 144.1, 147.5, 151.6, 158.0, 167.5. Anal. ($\text{C}_{27}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O} \cdot 1.5(\text{COOH})_2 \cdot 0.5\text{C}_3\text{H}_7\text{OH} \cdot 0.5\text{H}_2\text{O}$) C, H, N.

Example 6

***N*-(4-(4-(2,3-Dichloro-phenyl)-piperazin-1-yl)-*trans*-but-2-enyl)-4-(pyridin-*N*-oxide-2-yl)-benzamide (12).** Prepared from 4-(pyridin-*N*-oxide-2-yl)-benzoic acid and 4-(4-(2,3-dichloro-phenyl)-piperazin-1-yl)-*trans*-but-2-enylamine according to the general procedure. Yield: 27%. Mp. (oxalate): 153-154 °C. ^1H NMR (CDCl_3): δ 2.91 (s, br, 4H), 3.06 (m, 6H), 4.07 (m, 2H), 5.71-5.82 (m, 2H), 6.93-6.96 (m, 2H), 7.12-7.15 (m, 2H), 7.27-7.31 (m, 1H), 7.36 (t, J 7.54, 1H), 7.45 (d, J 7.83, 1.74, 1H), 7.86

(m, 4H), 8.33 (d, J 6.65, 0.78, 1H). ^{13}C NMR (CDCl_3): δ 41.8, 51.4, 53.4, 60.4, 118.9, 124.8, 125.4, 126.5, 127.3, 127.7, 127.7, 128.9, 129.7, 130.3, 134.2, 135.5, 135.6, 140.7, 148.7, 151.39, 166.9. Anal. ($\text{C}_{26}\text{H}_{26}\text{Cl}_2\text{N}_4\text{O}_2 \cdot 1.5(\text{COOH})_2$): C, H, N.

Example 7

4-(2,3-Dichlorophenyl)-1-(4-(4-(pyridin-2-yl)benzamido)-*trans*-but-2-enyl)-piperazine 1-oxide (13). A solution of PG01037, see U.S. 2006/0106030 (288 mg, 0.60 mmol) in 10 mL dichloromethane was treated at 0 °C with *meta*-chloroperbenzoic acid (0.16 g, 77%, 0.72 mmol). After stirring for 16 h at room temperature, the reaction mixture was successively washed with saturated sodium bicarbonate solution, H_2O and brine and dried with sodium sulphate. The volatiles were removed *in vacuo* and the residue was purified by preparative thin layer chromatography. Yield: 93 mg (32%). Mp. (hydrochloride): foam. ^1H NMR (CD_3OD): δ 3.23-3.29 (m, 4H), 3.50-3.61 (m, 4H), 3.99 (d, J 6.5, 1H), 4.13 (d, J 4.6, 1H), 6.04-6.18 (m, 2H), 7.18 (dd, J 7.8, 3.9, 1H), 7.24-7.28 (m, 2H), 7.40 (m, 1H), 7.91-7.93 (m, 2H), 7.99 (d, J 8.4, 2H), 8.06 (d, J 8.7, 2H), 8.64 (dt, J 4.8, 1.2, 1H). ^{13}C NMR (CDCl_3): δ 41.0, 45.5, 63.5, 72.0, 119.3, 120.0, 121.6, 123.1, 125.4, 127.0, 127.3, 127.7, 128.0, 133.8, 134.6, 137.8, 137.9, 142.2, 149.3, 150.1, 156.4, 168.3. Anal. ($\text{C}_{26}\text{H}_{26}\text{Cl}_2\text{N}_4\text{O}_2 \cdot 2\text{HCl} \cdot 0.5\text{H}_2\text{O}$) C, H, N.

Example 8

***N*-(4-(4-(2-Methoxy-phenyl)-piperazin-1-yl)-*trans*-but-2-enyl)-4-pyridin-2-yl-benzamide (14).** Prepared from 4-pyridin-2-yl-benzoic acid hydrochloride and 4-(4-(2-methoxyphenyl)-piperazin-1-yl)-*trans*-but-2-enyl amine according to the general procedure. Yield: 65%. Mp. (hydrochloride): 168-170°C. ^1H NMR (400 MHz, CDCl_3): δ 2.70 (s, 4H), 3.12 (s, 6H), 3.86 (s, 3H), 4.13 (m, 2H), 5.78-5.85 (m, 2H), 6.43 (m, 1H), 6.85-7.02 (m, 4H), 7.27 (s, 2H), 7.77 (s, 2H), 7.90 (d, J 7.5, 2H), 8.06 (d, J 8.1, 2H), 8.72 (d, J 3.1, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ 41.0, 50.9, 53.7, 55.8, 60.7, 111.6, 118.7, 121.3, 121.4, 123.2, 123.5, 127.5, 127.9, 129.1, 130.5, 135.0, 137.4, 141.6, 142.7, 150.3, 152.7, 156.7, 167.4. Anal. ($\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}_2 \cdot 3\text{HCl} \cdot 4\text{H}_2\text{O}$) C, H, N.

Example 9

***N*-(4-(4-(2-methoxyphenyl)piperazin-1-yl)-*trans*-but-2-enyl)-9*H*-fluorene-2-carboxamide (15).** Prepared from 9*H*-fluorene-2-carboxylic acid and 4-(4-(2-methoxyphenyl)-piperazin-1-yl)-*trans*-but-2-enyl amine according to the general

procedure. Yield: 61%. Mp. (hydrochloride): 224-226°C. ^1H NMR (400 MHz, CDCl_3): d 2.68 (s, 4H), 3.09-3.10 (m, 6H), 3.86 (s, 3H), 3.94 (s, 2H), 4.13 (m, 2H), 5.81-5.83 (m, 2H), 6.32 (t, J 5.4, 1H), 6.85 (dd, J 8.2, 1.2, 1H), 6.89-6.96 (m, 2H), 7.00 (m, 1H), 7.35 (td, J 7.3, 1.3, 1H), 7.40 (td, J 7.4, 1.6, 1H), 7.57 (d, J 7.4, 1H), 7.78-7.83 (m, 3H), 7.99 (s, 1H). ^{13}C NMR (101 MHz, CDCl_3): d 37.4, 42.0, 51.0, 53.8, 55.8, 60.8, 111.6, 118.7, 120.2, 121.0, 121.4, 123.4, 124.3, 125.7, 126.2, 127.5, 128.1, 129.3, 130.4, 133.1, 141.1, 141.7, 143.9, 144.5, 145.4, 152.7, 168.0. Anal. ($\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_2\cdot 3\text{HCl}$) C, H, N.

Example 10

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-4-pyridin-2-yl-benzamide (16).** Prepared from 4-pyridin-2-yl-benzoic acid hydrochloride and **27a** according to the general procedure. Yield: 52%. Mp. (hydrochloride): foam. ^1H NMR (CDCl_3): δ 1.62 (m, 1H), 1.83 (m, 1H), 2.39-2.46 (m, 2H), 2.58 (m, 2H), 2.82 (m, 2H), 3.05 (s, 4H), 3.45 (m, 1H), 3.89 (m, 2H), 4.00 (s, 1H), 6.91 (dd, J 7.1, 2.5, 1H), 7.08-7.15 (m, 2H), 7.23 (ddd, J 5.89, 4.83, 2.58, 1H), 7.50 (dd, J 5.9, 3.7, 1H), 7.70-7.76 (m, 2H), 7.88 (d, J 8.3, 2H), 8.02 (d, J 8.3, 2H), 8.67 (dt, J 4.8, 1.2, 1H). ^{13}C NMR (CDCl_3): δ 33.7, 38.8, 51.6, 53.5, 63.9, 66.6, 118.3, 120.5, 122.3, 124.3, 126.6, 127.1, 127.1, 133.6, 134.4, 136.4, 141.5, 149.3, 150.5, 155.7, 166.3. Anal. ($\text{C}_{26}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_2\cdot 2\text{HCl}\cdot 0.52\text{-PrOH}\cdot 1.5\text{H}_2\text{O}$) C, H, N.

Example 11

***N*-(3-(4-(2,3-Dichlorophenyl)-piperazin-1-yl)-3-hydroxybutyl)-9H-fluorene-2-carboxamide (17).** Prepared from 9H-fluorene-2-carboxylic acid and **27a** according to the general procedure. Yield : 58%. Mp. (oxalate): 188-190°C. ^1H NMR (oxalate, CDCl_3 , 5% D_2O) δ 1.60-1.69 (1H, m), 1.83-1.87 (1H, m), 2.42-2.50 (2H, m), 2.61 (2H, m), 2.86-2.87 (2H, m), 3.07 (4H, s), 3.45-3.52 (1H, m), 3.87-3.94 (4H, m), 6.94-8.00 (10H, m). ^{13}C NMR (oxalate, CDCl_3 , 5% D_2O) δ 33.6, 37.2, 38.6, 51.6, 53.5, 63.9, 66.7, 118.8, 119.9, 120.8, 124.1, 125.0, 125.4, 126.0, 127.2, 127.7, 127.8, 127.8, 133.1, 134.3, 141.0, 143.6, 144.3, 145.0, 151.3, 167.4, 167.8. Anal. ($\text{C}_{28}\text{H}_{29}\text{Cl}_2\text{N}_3\text{O}_2\cdot (\text{COOH})_2$), C, H, N.

Example 12

***N*-(3-Hydroxy-4-(4-(2-methoxy-phenyl)-piperazin-1-yl)-butyl)-4-pyridin-2-yl-benzamide (18).** Prepared from 4-pyridin-2-yl-benzoic acid hydrochloride and **27b** according to the general procedure. Yield: 47%. Mp. (oxalate): foam. ^1H NMR (CDCl_3): δ 1.63 (m, 1H), 1.84 (m, 1H), 2.43 (m, 2H), 2.64 (m, 2H), 2.88 (m, 2H), 3.11 (s, 4H), 3.46 (m, 1H), 3.86 (s, 3H), 4.94 (m, 2H), 6.86 (dd, J 7.4, 1.2, 1H), 6.92-6.94 (m, 2H), 7.01 (m, 1H), 7.23 (m), 7.52 (dd, J 5.9, 3.7, 1H), 7.74-7.79 (m, 2H), 7.91 (d, J 8.3, 2H), 8.05 (d, J 8.3, 2H), 8.71 (dt, J 4.8, 1.2, 1H). ^{13}C NMR (CDCl_3): δ 33.0, 38.3, 50.5, 53.2, 55, 63.5, 66.3, 110.9, 117.9, 120.6, 120.7, 122.4, 122.8, 126.7, 127.2, 134.6, 136.6, 140.8, 141.7, 149.6, 152.0, 156.1, 166.7. Anal. ($\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}_2(\text{COOH})_2 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

Example 13

***N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)-butyl)-9H-fluorene-2-carboxamide (19).** Prepared from 9H-fluorene-2-carboxylic acid and **27b** according to the general procedure. Yield: 45%. Mp. (oxalate): foam. (^1H NMR (CDCl_3): δ 1.64 (m, 1H), 1.83 (m, 1H), 2.43 (m, 2H), 2.87 (m, 2H), 3.10 (s, 4H), 3.47 (m, 1H), 3.86 (s, 3H), 3.89-3.99 (m, 6H), 6.86 (d, J 7.4, 1H), 6.91-6.94 (m, 2H), 7.01 (m, 1H), 7.32-7.41 (m, 2H), 7.45 (dd, J 5.9, 3.5, 1H), 7.55 (d, J 7.4, 1H), 7.77-7.83 (m, 3H), 8.00 (s, 1H). ^{13}C NMR (CDCl_3): δ 33.3, 36.9, 38.5, 50.7, 55.3, 63.8, 66.6, 111.1, 118.1, 119.6, 120.5, 120.9, 123.1, 123.8, 125.2, 125.8, 126.9, 127.5, 133.0, 140.7, 141.0, 143.3, 144.0, 144.6, 152.2, 167.5. Anal. ($\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_3(\text{COOH})_2 \cdot \text{H}_2\text{O}$) C, H, N.

Example 14

1-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-4-(4-(pyridin-2-yl)-benzamido)-butan-2-yl acetate (20). A solution of **16** (0.25 g, 0.5 mmol) in 10 mL of CH_2Cl_2 was treated with 70 μL (0.75 mmol) acetic anhydride followed by 140 μL (1.0 mmol) triethylamine. After stirring for 16 h, the mixture was washed with sodium bicarbonate solution, dried with sodium sulphate and purified by flash chromatography. Yield: 0.22 g (82%). Mp. (oxalate): foam. ^1H NMR (CDCl_3): δ 1.84 (m, 1H), 2.05 (m, 1H), 2.12 (s, 3H), 2.52 (dd, J 13.2, 5.2, 1H), 2.65 (m, 5H), 2.99 (s, 4H), 3.25 (dq, J 9.7, 5.00, 1H), 3.81 (dt, J 12.3, 5.7, 1H), 5.19 (m, 1H), 6.89 (dd, J 7.7, 1.8, 1H), 7.06-7.17 (m, 3H), 7.26 (ddd, J 6.1, 4.8, 2.44, 1H), 7.73-7.76 (m, 2H), 7.93 (d, J 8.6, 2H), 8.07 (d, J 8.6, 2H), 8.70 (td, J 4.83, 1.50, 1.50, 1H). ^{13}C NMR

(CDCl₃): δ 21.0, 32.4, 36.1, 51.3, 53.7, 61.5, 69.6, 118.6, 120.8, 122.7, 124.5, 127.0, 127.4, 127.5, 133.9, 134.7, 136.9, 142.1, 149.8, 151.1, 156.2, 167.1, 171.5, Anal. (C₂₈H₃₀Cl₂N₄O₃·1.5(COOH)₂·H₂O) C, H, N.

Example 15

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-hydroxybutyl)-4-(pyridin-2-yl)-benzamide (21).** Prepared from 4-pyridin-2-yl-benzoic acid and **30a** according to the general procedure. Yield: 52%. Mp. (oxalate): foam. ¹H NMR (CDCl₃): δ 1.63 (ddd, *J* 14.6, 6.0, 3.4, 1H), 1.81 (dtd, *J* 14.5, 10.9, 10.8, 3.9, 1H), 2.72 (m, 6H), 3.07 (s, 4H), 3.34 (ddd, *J* 13.4, 7.6, 4.6, 1H), 3.77 (ddd, *J* 13.4, 6.7, 3.4, 1H), 4.07 (m, 1H), 6.77 (t, *J* 5.3, 1H), 6.93 (dd, *J* 7.4, 2.2, 1H), 7.13-7.19 (m, 2H), 7.28 (m, 1H), 7.76-7.81 (m, 2H), 7.91 (d, *J* 8.6, 2H), 8.07 (d, *J* 8.6, 2H), 8.72 (td, *J* 4.8, 1.4, 1.4, 1H). ¹³C NMR (CDCl₃): δ 28.8, 45.8, 51.4, 53.3, 57.5, 72.7, 118.7, 120.9, 122.8, 125.0, 127.1, 127.5, 127.6, 127.7, 134.2, 134.8, 137.0, 142.2, 149.9, 150.9, 156.3, 167.3. Anal. (C₂₆H₂₈Cl₂N₄O₂·(COOH)₂·H₂O), C, H, N.

Example 16

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-hydroxybutyl)-9H-fluorene-2-carboxamide (22).** Prepared from 9H-fluorene-2-carboxylic acid and **30a** according to the general procedure. Yield: 68%. Mp. (oxalate): foam. ¹H NMR (CDCl₃): δ 1.63 (m, 1H), 1.78 (m, 1H), 2.63 (s, 2H), 2.72-2.84 (m, 2H), 2.87 (s, 2H), 3.07 (s, 4H), 3.34 (m, 1H), 3.77 (ddd, 13.7, 7.0, 3.5, 1H), 3.94 (s, 2H), 4.07 (m, 1H), 6.90 (dd, *J* 5.4, 2.0, 1H), 7.12-7.18 (m, 2H), 7.36 (t, *J* 5.3, 1H), 7.37 (t, *J* 5.4, 1H), 7.41 (d, *J* 7.0, 1H), 7.81-7.82 (m, 3H), 8.00 (s, 1H). ¹³C NMR (CDCl₃): δ 28.9, 37.0, 45.9, 51.4, 53.4, 57.5, 72.8, 118.7, 119.8, 120.7, 124.0, 125.0, 125.3, 126.0, 127.1, 127.6, 127.7, 127.8, 133.0, 134.2, 140.8, 143.6, 144.2, 145.0, 150.9, 168.0. Anal. (C₂₈H₂₉Cl₂N₃O₂·2.5HCl·0.5EtOAc·1.75H₂O) C, H, N.

Example 17

***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)-2-hydroxybutyl)-9H-fluorene-2-carboxamide (23).** Prepared from 9H-fluorene-2-carboxylic acid and **30b** according to the general procedure. Yield: 42%. Mp. (oxalate): foam. ¹H NMR (CDCl₃): δ 1.62 (ddd, *J* 9.9, 6.1, 3.4, 1H), 1.80 (m, 1H), 2.63 (s, 2H), 2.76 (m, 2H), 2.88 (s, 2H), 3.10 (s, 4H), 3.33 (ddd, *J* 13.4, 7.7, 4.5, 1H), 3.78 (ddd, *J* 13.4, 6.8, 3.4, 1H), 3.80 (s, 3H), 3.91 (s, 2H), 4.06 (m, 1H), 6.83-6.87 (m, 2H), 6.89-6.92 (m, 2H), 7.01 (ddd, *J* 8.0,

5.8, 3.3, 1H), 7.34 (td, *J* 7.4, 1.3, 1H), 7.39 (td, *J* 7.5, 1.3, 1H), 7.55 (d, *J* 7.5, 1H), 7.79 (dd, *J* 7.9, 0.5, 1H), 7.82 (dd, *J* 8.1, 1.5, 1H), 8.00 (d, *J* 0.7, 1H). ¹³C NMR (CDCl₃): δ 28.8, 36.9, 45.8, 50.6, 53.5, 55.4, 57.4, 72.6, 111.2, 118.2, 119.7, 120.6, 121.0, 123.2, 123.9, 125.2, 125.9, 127.0, 127.6, 132.9, 140.7, 140.8, 143.4, 144.0, 144.8, 152.2, 167.9. Anal. (C₂₉H₃₃N₃O₃·(COOH)₂·1.25H₂O) C, H, N.

Example 18

2-(Oxiran-2-yl)-ethyl-isoindoline-1,3-dione (25). A suspension of 1.84 g (10.0 mmol) phthalimid potassium salt in 20 mL DMF was treated with 2.27 g (15.0 mmol) **24** in the microwave (pressure vessel, P_{max} 150 W, cooling, 100 °C, 20 min). See *J. Org. Chem.* **1969**, 34, 4060-4065. The cooled reaction mixture was filtered, diluted with EtOAc (20 mL) and was washed with H₂O (2 x 10 mL). The organic phase was dried with sodium sulphate and the volatiles were removed *in vacuo* to give **25** (1.68 g, 78%) as a foam, which was used without further purification. ¹H NMR (CDCl₃): δ 1.86 (m, 1H), 2.00 (m, 1H), 2.46 (m, 1H), 2.73 (t, *J* 3.9, 1H), 3.00 (m, 1H), 3.89 (m, 2H), 7.70-7.74 (m, 2H), 7.83-7.87 (m, 2H). ¹³C NMR (CDCl₃): δ 31.7, 35.2, 46.5, 50.4, 123.4, 132.2, 134.1, 168.4.

Example 19

2-(4-(4-(2,3-Dichlorophenyl)-piperazin-1-yl)-3-hydroxybutyl)-isoindoline-1,3-dione (26a). A sample of 2.1g (9.0 mmol) 1-(2,3-dichlorophenyl)-piperazine in 40 mL 2-PrOH was reacted in the microwave (pressure vessel, P_{max} 150 W, cooling, 90 °C, 20 min) with 2.0 g (9.0 mmol) **25**. The solvent was removed *in vacuo* and the foamy residue was washed with 10 mL 2-PrOH. Yield: 2.96 g (73%). ¹H NMR (CDCl₃): δ 1.79 (m, 2H), 2.42 (m, 2H), 2.56 (s, 2H), 2.79 (m, 2H), 3.02 (s, 4H), 3.60 (s, 1H), 3.74-3.83 (m, 3H), 6.90 (m, 1H), 7.06-7.11 (m, 2H), 7.67 (m, 2H), 7.81 (m, 2H). ¹³C NMR (CDCl₃): δ 33.9, 35.3, 51.4, 53.4, 63.8, 64.5, 118.2, 122.7, 124.1, 127.0, 131.6, 133.4, 133.4, 150.4, 167.7.

Example 20

2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione (26b). Prepared from 1-(2-methoxyphenyl)piperazine and **25** in a similar fashion as described above for **26a**. Yield: 28%. Mp.: 192-194 °C. ¹H NMR (CDCl₃): δ 1.79 (q, *J* 6.8, 2H), 2.41 (m, 2H), 2.61 (s, 2H), 2.85 (s, 2H), 3.07 (s, 4H), 3.77 (m, 1H), 3.85 (s, 3H), 3.91 (m, 2H), 6.86 (d, *J* 7.0, 1H), 6.91-6.95 (m, 2H), 7.00 (m, 1H),

7.85 (dd, J 5.5, 3.0, 2H), 7.71 (dd, J 5.4, 3.1, 2H). ^{13}C NMR (CDCl_3): δ 33.8, 35.4, 50.9, 53.6, 55.6, 64.1, 64.7, 111.3, 118.4, 121.2, 123.2, 123.4, 132.4, 134.1, 141.4, 152.4.

Example 21

4-Amino-1-(4-(2,3-dichlorophenyl)piperazin-1-yl)-butan-2-ol (27a). A sample of 4.48 g (10.0 mmol) **26a** was fully dissolved in 25 mL EtOH and treated with 0.48 g (15.0 mmol) hydrazine in the microwave (pressure vessel, P_{max} 150 W, cooling, 90 °C, 20 min). The cooled reaction mixture was filtered and the filtrate was evaporated *in vacuo*. Both the residue from the evaporation and the initial precipitate were partitioned between CHCl_3 and 20% potassium carbonate solution. The layers were separated and the aqueous layer was dried with sodium sulphate to give the title compound as an oil, which was used without further purification. Yield: 2.25 g (71%). ^1H NMR (CDCl_3): δ 1.56 (m, 2H), 2.40 (m, 2H), 2.61 (s, 2H), 2.80 (s, 2H), 2.97-3.05 (m, 9H), 3.89 (m, 1H), 6.92 (dd, J 6.3, 3.1, 1H), 7.09-7.14 (m, 2H). ^{13}C NMR (CDCl_3): δ 37.4, 39.7, 51.5, 53.6, 64.5, 66.3, 118.3, 124.2, 127.1, 133.5, 150.6.

Example 22

4-Amino-1-(4-(2-methoxy-phenyl)-piperazin-1-yl)-butan-2-ol (27b). Prepared from **26b** in a similar fashion as described above for **27a**. Yield: 69%. Wax. ^1H NMR (CDCl_3): δ 1.59 (m, 2H), 2.41 (m, 2H), 2.57 (m, 2H), 2.79-2.81 (m, 9H), 3.86 (s, 3H), 3.91 (m, 1H), 6.86 (d, J 7.5, 1H), 6.91-6.96 (m, 2H), 6.98-7.03 (m, 1H). ^{13}C NMR (CDCl_3): δ 37.3, 39.7, 50.9, 53.6, 55.5, 64.5, 66.2, 111.2, 118.3, 121.1, 123.1, 141.3, 152.3.

Example 23

1-(2,3-Dichlorophenyl)-4-(2-(oxiran-2-yl)ethyl)piperazine (28a). 2.31 g (10.0 mmol) 1-(2,3-dichlorophenyl)piperazine was added to a suspension of 2.27 g (15.0 mmol) **24**, 4.15 g (30.0 mmol) potassium carbonate in 150 mL acetone and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered and the volatiles were removed *in vacuo* to give an oil (2.86 g, 95%), which was used without further purification. ^1H NMR (CDCl_3): δ 1.72 (m, 1H), 1.83 (m, 1H), 2.53 (dd, J 5.0, 2.7, 1H), 2.61 (ddd, J 8.3, 6.5, 3.0, 2H), 2.66 (s, 4H), 2.79 (dd, J 4.9, 4.0, 1H), 3.01 (m, 1H), 3.07 (s, 4H), 6.96 (dd, J 6.5, 3.1, 1H), 7.11-7.19 (m, 2H). ^{13}C NMR (CDCl_3): δ 30.2, 47.1, 51.0, 51.4, 53.3, 55.0, 118.6, 124.6, 127.5, 134.0, 151.3.

Example 24

1-(2-Methoxyphenyl)-4-(2-(oxiran-2-yl)ethyl)piperazine (28b). Prepared from **24** and 1-(2-methoxyphenyl)piperazine in a similar fashion as described above for **28a**. Yield: 87%. ¹H NMR (CDCl₃): δ 2.60 (m, 2H), 2.67 (s, 4H), 2.78 (dd, *J* 4.9, 4.0), 3.00 (m, 1H), 3.10 (s, 4H), 3.86 (s, 3H), 6.86 (dd, *J* 7.8, 1.3, 1H), 6.88-7.03 (m, 3H). ¹³C NMR (CDCl₃): δ 30.2, 47.2, 50.7, 51.0, 53.5, 55.2, 55.4, 111.2, 118.3, 121.1, 123.0, 141.4, 152.3.

Example 25

1-Azido-4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (29a). A suspension of 0.75 g (2.5 mmol), 0.24 g (3.8 mmol) sodium azide and 0.27 g (5.0 mmol) ammonium chloride in 5 mL DMF was heated at 100 °C for 5h. The reaction mixture was partitioned between 10 mL CHCl₃ and 10 mL H₂O. The aqueous organic layer was extracted twice with 10 mL CHCl₃, dried over sodium sulphate and the volatiles were removed *in vacuo*. The residue was purified by flash chromatography to give the **29a** as an oil. Yield: 0.44g (51%). ¹H NMR (CDCl₃): δ 1.56 (ddd, *J* 14.7, 6.5, 3.4, 1H), 1.81 (m, 1H), 2.62 (s, 2H), 2.75 (m, 2H), 2.87 (s, 2H), 3.07 (s, 4H), 3.27 (dd, *J* 5.1, 1.4, 2H), 4.04 (dtd, *J* 7.9, 5.3, 2.6, 1H), 6.52 (s, 1H), 6.93 (dd, *J* 7.2, 2.4, 1H), 7.12-7.19 (m, 2H). ¹³C NMR (CDCl₃): δ 28.4, 51.3, 53.3, 56.5, 57.3, 73.0, 118.7, 124.9, 127.6, 134.1, 150.9.

Example 26

1-Azido-4-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol. Prepared from **28b** in a similar fashion as described above for **29a**. Yield: 15%. ¹H NMR (CDCl₃): δ 1.55 (ddd, *J* 14.6, 6.7, 3.6, 1H), 1.80 (m, 1H), 2.62 (s, 2H), 2.74 (m, 2H), 2.89 (s, 2H), 3.09 (s, 4H), 3.24 (dd, *J* 11.6, 4.1, 1H), 3.29 (dd, *J* 11.6, 4.9, 1H), 3.86 (s, 3H), 4.03 (dtd, *J* 9.8, 5.5, 2.5, 1H), 6.86 (d, *J* 8.0, 1H), 6.89-6.95 (m, 2H), 7.01 (ddd, *J* 8.0, 5.1, 4.1, 1H). ¹³C NMR (CDCl₃): δ 28.4, 50.7, 53.5, 53.5, 55.4, 56.6, 57.4, 73.0, 111.2, 118.3, 121.1, 123.2, 140.9, 152.3.

Example 27

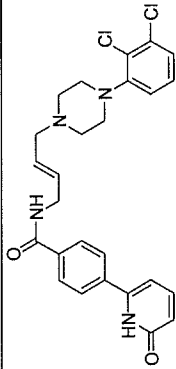
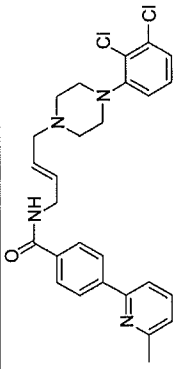
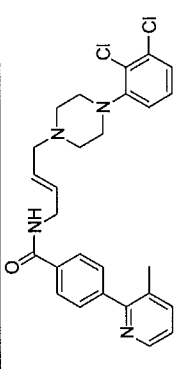
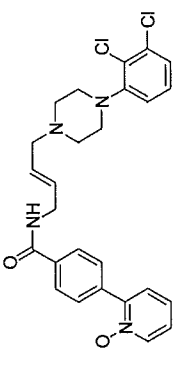
1-Amino-4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (30a). A solution of **29a** (0.41 g, 1.2 mmol) and 1.87g (7.2 mmol) triphenylphosphine in 20 mL of a THF/H₂O mixture (10:1 v/v) was stirred at room temperature for 16 h. The volatiles were removed *in vacuo* and the residue was taken up in 2-PrOH (5 mL) and

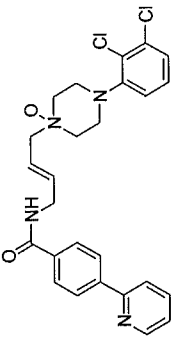
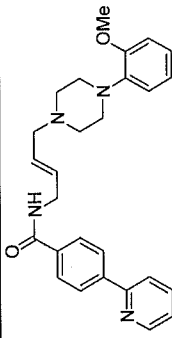
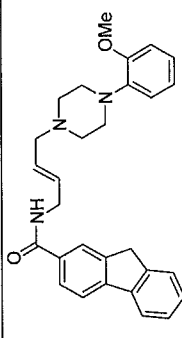
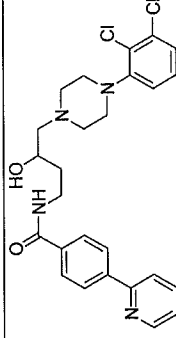
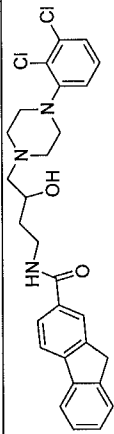
treated with ethereal hydrochloric acid to give desired amine as a hydrochloride (0.33 g, 77%). ^1H NMR (CDCl_3): δ 1.53 (ddd, J 14.5, 6.8, 4.0, 1H), 1.71 (m, 1H), 2.61 (s, 2H), 2.65-2.77 (m, 4H), 2.84 (s, 2H), 3.07 (m, 4H), 3.77 (m, 1H), 6.93 (dd, J 7.0, 2.5, 1H), 7.12-7.17 (m, 2H). ^{13}C NMR (CDCl_3): δ 29.0, 48.3, 51.3, 53.3, 74.9, 118.6, 124.8, 127.5, 134.0, 150.9.

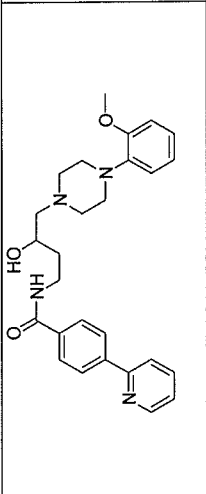
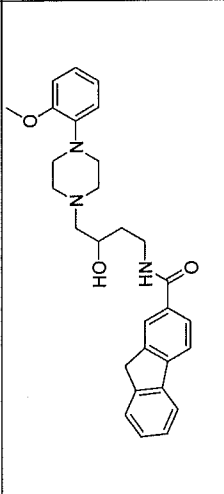
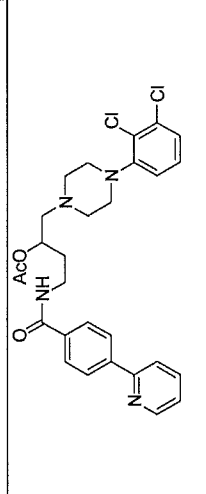
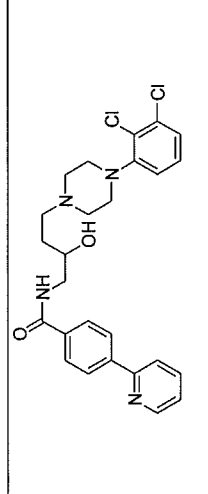
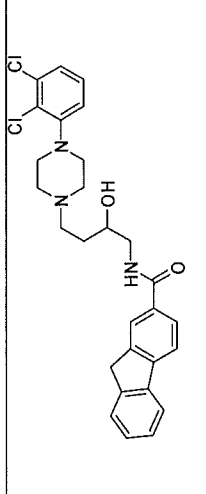
Example 28

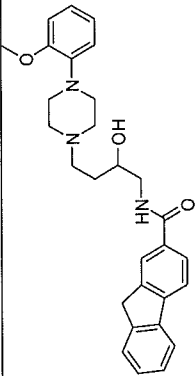
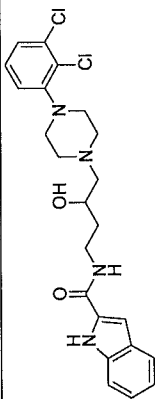
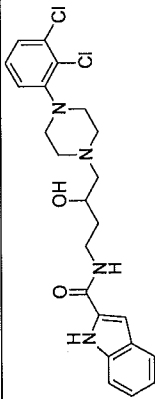
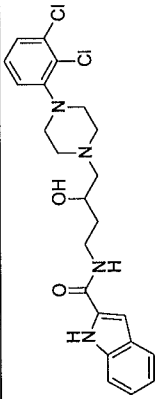
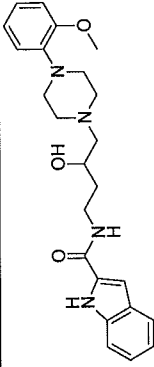
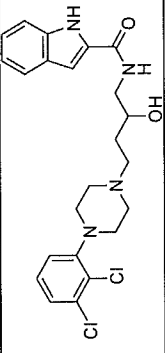
1-Amino-4-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (30b). Prepared from **29b** in a similar fashion as described above for **30a**. Yield: 13 %. ^1H NMR (CDCl_3): δ 1.52 (ddd, J 14.5, 6.5, 3.9, 1H), 1.71 (m, 1H), 2.54-2.77 (m, 4H), 2.86 (s, 2H), 3.09 (s, 4H), 3.77 (m, 1H), 3.87 (s, 3H), 6.86 (d, J 7.9, 1H), 6.90-6.95 (m, 2H), 7.00 (m, 1H). ^{13}C NMR (CDCl_3): δ 29.0, 48.4, 50.7, 53.6, 55.4, 57.6, 75.2, 111.2, 118.3, 121.1, 123.2, 141.0, 152.3.

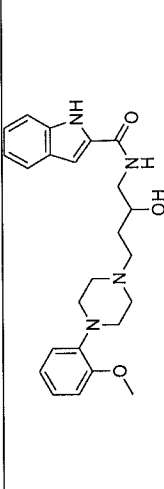
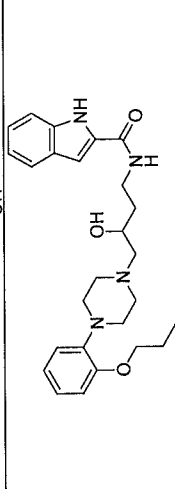
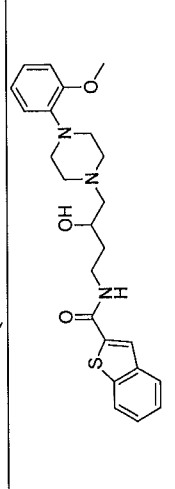
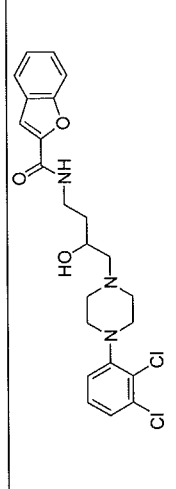
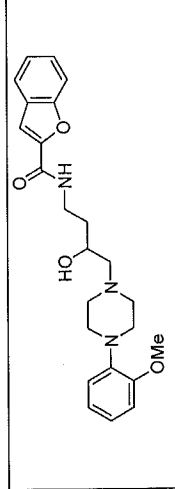
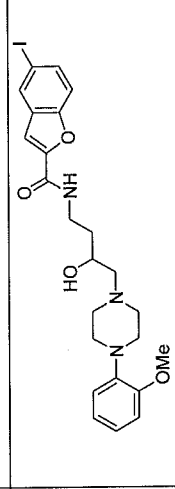
Table 1. Human D₂-like Family Receptor Subtype Binding Data in HEK Cells

Compd.	structure	D2	SEM	D3 K _i [nM]	SEM	D4	SEM	D2/D3	D4/D2
9		23.6	5.7	0.6	0.1			39	
10		105	24	1.4	0.3			75	
11		92.0	9.4	1.6	0.4			58	
12		25.8	3.1	1.1	0.3			23	

13		1160	230	49.2	9.3			24	
14		69.0	13	2.9	1.1			24	
15		48.4	7.3	1.2	0.1			40	
16		267	20	3.0	0.2	4620	200	89	1540
17		319	54	1.8	0.0	16400	2600	177	9110

18		284	48	2.8	0.8	1490	150	101	532
19		249	14	1.8	0.3	1230	330	138	683
20		134	28	11.7	1.0			11	
21		28.4	6.4	0.5	0.1			57	
22		84.0	5.3	2.5	0.3			34	

23		68.4	6.4	1.3	0.4			53	
34		200	52	0.9	0.3			225	
34 Enantiomer A		441	52	1.1	0.3			400	
34 Enantiomer B		1083	379	16.5	3.2			65	
35		248.6	62.7	1.37	0.2	1919	373	181	1401
36		28.4	6.5	0.26	0.06			109	

37		52.5	4.5	0.5	0.03		105	
38		47.1	7.4	62.1	3.1		1	
39		337	21.7	4.6	0.6		73	
42		185		0.98			188	
43		233		5.4			43	
44		158		2.2			71	

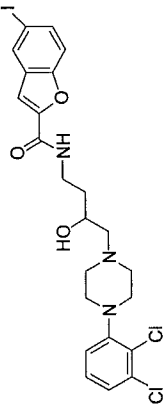
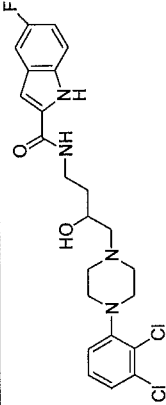
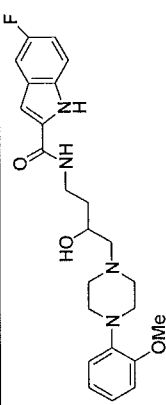
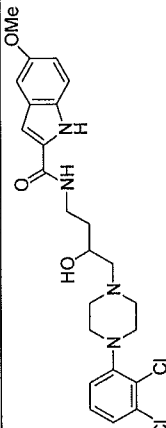
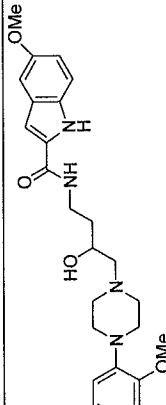
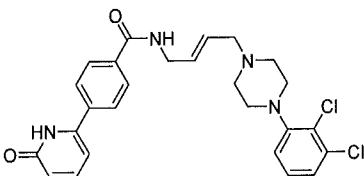
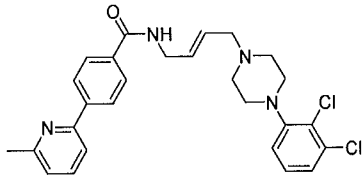
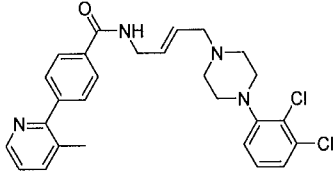
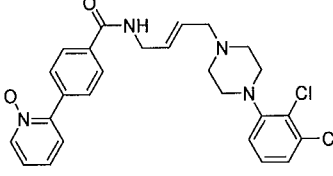
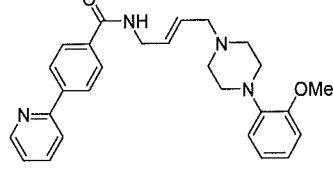
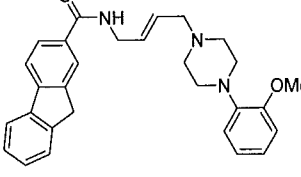
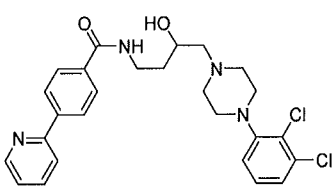
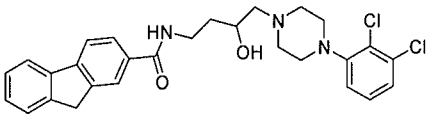
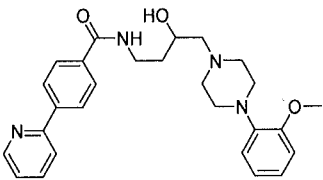
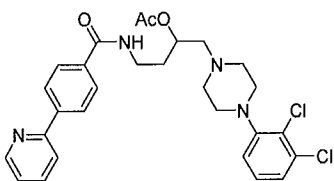
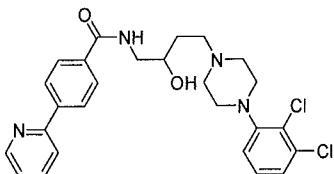
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46		245			1.6				149	
47		180			0.65				276	
48		244			1.3				185	
49		174			1.0				172	

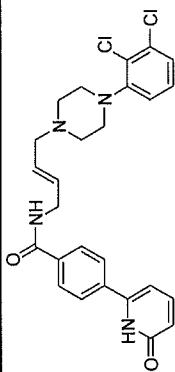
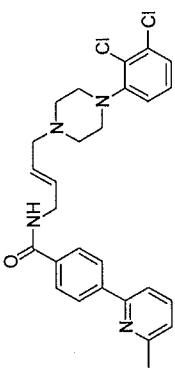
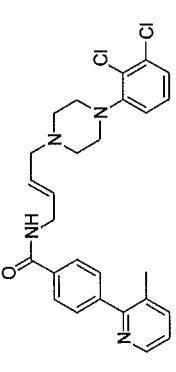
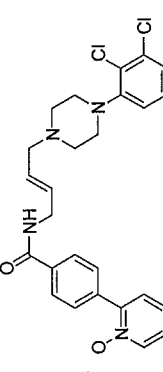
Table 2. In Vitro Functional Data at D₂-like Family Receptor for selected ligands^a

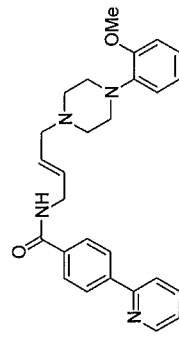
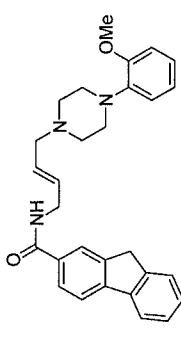
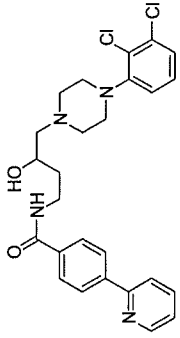
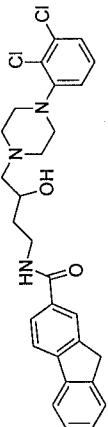
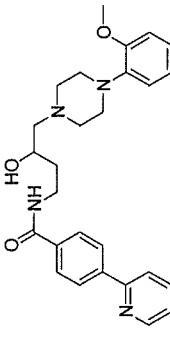
Compd.	structure	D2	D3
		IC ₅₀ (nM) ± S.E.M.	
9		41 ± 8	1.0 ± 0.2
10		1300 ± 320	6.7 ± 2.6
11		368 ± 113	25.6 ± 8.5
12		22.9 ± 2.0 231 ± 1 (31) ^b	1.2 ± 0.0
14		175 ± 17	42.6 ± 7.9
15		179 ± 48	18.9 ± 4.2

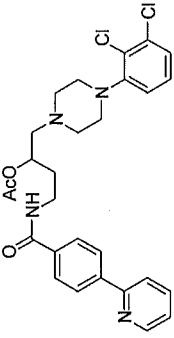
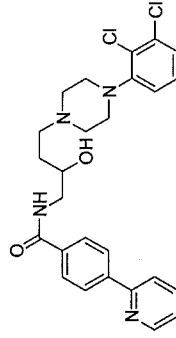
16		15.8 ± 2.7 (26) ^b	1.0 ± 0.1 (48) ^b
17		ND	42.0 ± 1.3 (26) ^b
18		ND	12.8 ± 1.3
20		ND	3.9 ± 1.4 (47) ^b
21		88.3 ± 15.7	5.4 ± 1.8 3.4 ± 0.5 (20) ^b

^aData were obtained through the NIDA Addiction Treatment Discovery Program contract with SRI (N01DA-1-8816). ^b partial agonist activity: EC₅₀ (% stimulation) ^a

Table 3. Binding affinities for a serotonin receptor subtypes for selected ligands.^a

Compd.	structure	K _i (nM) ±S.E.M.						
		5HT _{1A}	5HT _{2A}	5HT _{2C}	D ₃	5HT _{1A} /D3	5HT _{2A} /D3	5HT _{2C} /D
9		29.7 ± 0.2	15.5 ± 3.8	10.6 ± 0.0	0.6 ± 0.1	50	26	18
10		309 ± 39	92.7 ± 16	96.4 ± 1.1	1.4 ± 0.3	221	66	69
11		92 ± 8.3	46.9 ± 5.4	31 ± 2.3	1.6 ± 0.4	58	29	19
12		60.6 ± 4.3	57.9 ± 0.6	74.3 ± 3	1.1 ± 0.3	55	53	68

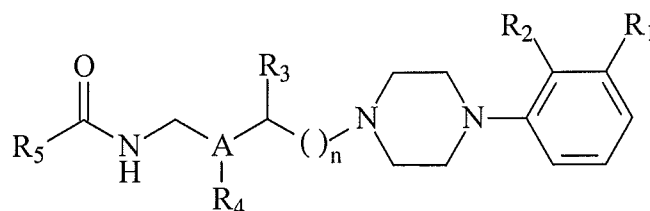
14		21.7 ± 3.5	75.3 ± 1.1	256 ± 33	2.9 ± 1.1	7	26	88
15		71.8 ± 2.1	65.7 ± 12	176 ± 14	1.2 ± 0.1	60	55	147
16		34.3 ± 0.3	42.3 ± 9.1	115 ± 20	3.0 ± 0.2	11	14	38
17		1810 ± 350	545 ± 150	2830 ± 360	1.8 ± 0.0	1006	303	1572
18		36.2 ± 7	695 ± 20	3940 ± 130	2.8 ± 0.8	13	248	1407

	117 ± 12	88.7 ± 7.5	84.3 ± 5.3	11.7 ± 1.0	10	7	7
	15.1 ± 2.4	15.4 ± 2.8	25.2 ± 3.2	0.5 ± 0.1	30	31	50

^aData were obtained through the NIDA Addiction Treatment Discovery Program contract with SRI (N01DA-1-8816).

We claim:

1. A chemical compound of the following chemical formula:



Wherein:

A = trans CH=CH or C;

n = 0 or 1;

R₁ and R₂ = independently represent hydrogen, halogen, or alkoxy;

R₃ and R₄ = H, OH, OAc, alkoxy, halogen, amino, nitro, alkoxy, alkyl, acyl and pyridyl;

R₅ = phenyl, indole, thiophene, benzofuran, fluorenyl, or 2-pyridylphenyl; and R₅ is optionally substituted with one or more of hydrogen, halogen, amino, nitro, hydroxyl, alkoxy, alkyl, acyl and pyridyl, substitution may occur at any of the ortho, meta, or para positions;

including all enantiomers and pharmaceutical salts thereof.

2. The compound of claim 1 in which A is C.

3. The chemical compound of claim 1 that is: N-(3-Hydroxy-4-(4-(2-methoxyphenyl)-piperazin-1-yl)-butyl)-4-pyridin-2-yl-benzamide.

4. The chemical compound of claim 1 that is: N-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)-butyl)-9H-fluorene-2-carboxamide.

5. The chemical compound of claim 1 that is: N-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-1H-indole-2-carboxamide.

6. The chemical compound of claim 1 that is: N-(3-hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1H-indole-2-carboxamide.

7. The chemical compound of claim 1 that is: N-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-5-iodo- or 5-fluorobenzofuran-2-carboxamide.

8. The chemical compound of claim 1 that is: 5-fluoro-N-(3-hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1H-indole-2-carboxamide.

9. A method of treating an addiction comprising: administering a pharmaceutically effective amount of a compound of claim 1 to a patient in need thereof.

10. A method of treating schizophrenia or Parkinson's disease or dyskinesias associated with these diseases comprising: administering a pharmaceutically effective amount of a compound of claim 1 to a patient in need thereof.

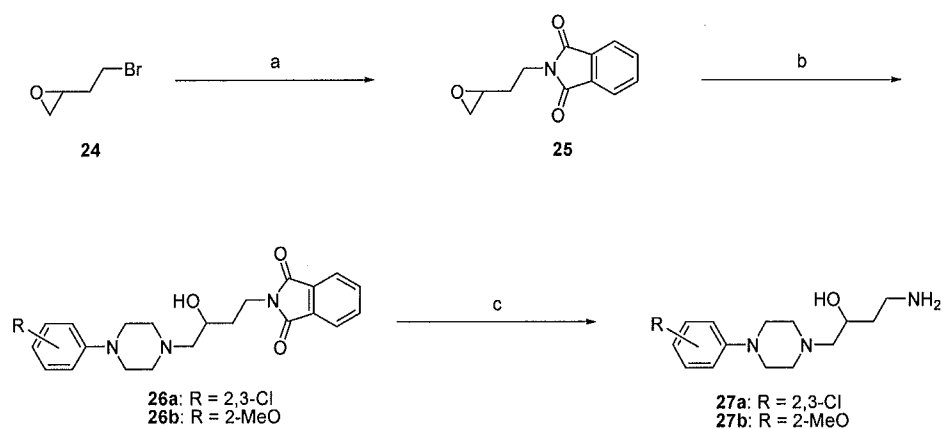
11. A method of selectively imaging dopamine D₂ family binding sites of the central nervous system to detect or monitor a disease resulting from abnormal distribution and/or density of dopamine D₃ receptor in the central nervous system of a patient comprising:

- i) contacting central nervous system tissue with a compound of claim 1; and
- ii) detecting the binding of the compound to the central nervous system tissue.

12. The method of claim 11, further comprising:

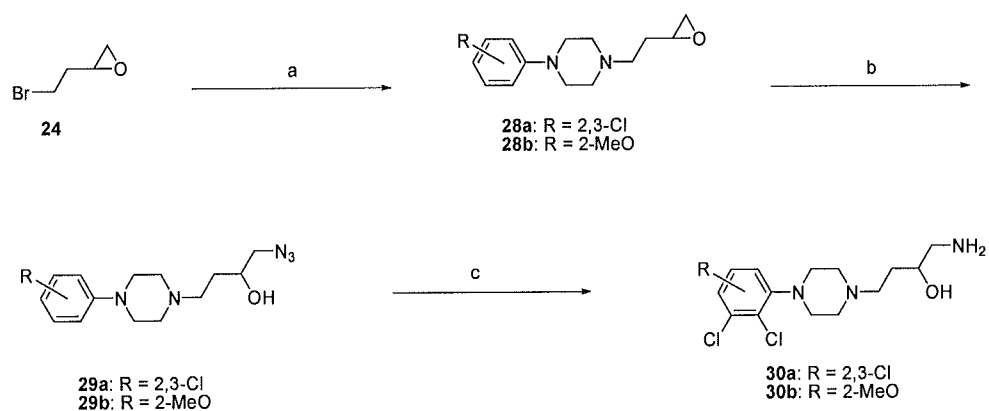
- iii) determining the distribution and/or density of the dopamine D₃ receptor in the central nervous system tissue;
- iv) comparing the distribution and/or density obtained with the distribution and/or density of dopamine D₃ receptor in a corresponding normal tissue; and
- v) diagnosing a disease state by a difference in the distribution and/or density between the normal tissue and the subject tissue.

Figure 1

Synthesis of the 3-hydroxyl amines **27^a**

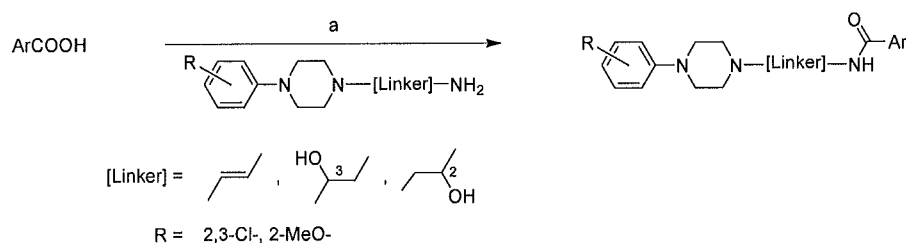
^a Reagents and conditions: (a) phthalimid potassium salt, DMF, microwave, 100 °C, 20 min; (b) 1-(2,3-dichlorophenyl)- or 1-(2-methoxyphenyl)-piperazine, 2-PrOH, microwave, 90 °C, 20 min; (c) hydrazine, ethanol, microwave, 90 °C, 20 min.

Figure 2

Synthesis of the 2-hydroxyl amines **30**^a

^a Reagents and conditions: (a) 1-(2,3-dichlorophenyl)- or 1-(2-methoxyphenyl)-piperazine, potassium carbonate, acetone, reflux, 24 h; (b) sodium azide, ammonium chloride, DMF, 100 °C; 4 h; (c) triphenyl phosphine, THF, room temperature, 16 h.

Figure 3

Synthesis of Compounds **9-23** and **34-49**^a

^a Reagents and conditions: (a) CDI, pyridine or DCC, HOBT, DMF. **13** was prepared from *N*-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)but-2-enyl)-4-(pyridin-2-yl)benzamide; PG01037 by *N*-oxidation (mCPBA, CH₂Cl₂, room temperature, 16 h). **20** was prepared from **16** by acetylation (NEt₃, CH₃COCl, room temperature, 16 h).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/071412**A. CLASSIFICATION OF SUBJECT MATTER***C07D 295/145(2006.01)i, C07D 401/12(2006.01)i, A61P 25/00(2006.01)i*

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)

IPC 8 C07D 295/145, C07D 401/12, A61P 25/00

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)

STN (Registry, CAplus)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006-072608 A (UNIVERSITA DEGLI STUDI DI SIENA) 13 July 2006 See table 1; claims; compounds. 1-7, 1-8 1-22, 1-24, 1-31, 1-32, 1-45, 1-46.	1-8
X	GRUNDT, P. et al. 'Novel Heterocyclic trans Olefin Analogues of N-{4-[4-(2,3-Dichlorophenyl) piperazin-1-yl]butyl} arylcarboxamides as Selective Probe with High Affinity for the Dopamine D3 receptor.' J. Med. Chem. 2005, Vol. 48, No. 3, pp. 839-848, ISSN 0022-2623. See tables 1-4, compounds 1-38, abstract.	1-8
X	WO 2004-024878 A (GOV'T OF THE U.S.A. AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES) 25 March 2004 See abstract, tables 1-3.	1-8

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

03 MARCH 2008 (03.03.2008)

Date of mailing of the international search report

03 MARCH 2008 (03.03.2008)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 139 Seonsa-ro, Seo-
gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

SUNG Sun Young

Telephone No. 82-42-481-8405



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2007/071412

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NEWMAN, A. H. et al. 'N- {4-[4-2,3-Dichlorophenyl]piperazin-1-yl]butyl, Butenyl and Butynyl} arylcarboxamides as Novel Dopamine D3 Receptor Antagonists' Bioorganic & Medicinal Chemistry Letter 2003, Vol. 13, No. 13, pp. 2179-2183, ISSN 0960-894X See compounds 1-35, figures 1-3, tables 1-4	1-8
X	WO 2004-004729 A (FRIEDRICH-ALEXANDER-UNIVERSITAET ERLANGEN-NUERNBERG) 15 January 2004 See examples 3-6, 10, 12, 14, 24, table 1, claims	1-8
Y	WO 2006-050976 A (SCHWARZ PHARMA AG.) 18 May 2006 See abstract, examples	1-8
Y	WO 2006-015737 A (SCHWARZ PHARMA AG.) 16 February 2006 See abstract, examples	1-8
Y	WO 1998-06717 A (NEUROGEN CORPORATION) 19 February 1998 See abstract, examples	1-8
Y	WO 1997-31916 A (NEUROGEN CORPORATION) 04 September 1997 See abstract, examples	1-8
Y	WO 1997-34889 A (NEUROGEN CORPORATION) 25 September 1997 See abstract, claims	1-8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2007/071412**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.: 9-12
because they relate to subject matter not required to be searched by this Authority, namely:
The claims pertain to methods for treatment of the human or animal body by therapy or diagnostic methods, and thus relate to a subject matter which this international Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
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:

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 fee, this Authority did not invite payment of any additional fee.
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.:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2007/071412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006-072608 A	13.07.2006	AU 2006204522 AA CA 2593266 AA EP 1836192 A2 WO 2006-072608 A3	13.07.2006 13.07.2006 26.09.2007 28.09.2006
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2007/071412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 1997-34889 A	25.09.1997	None	