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(54) **6-METHOXY-8-[4-(1-(5-FLUORO)-QUINOLIN-8-YL-PIPERIDIN-4-YL)-PIPERAZIN-1-YL]-QUINOLINE HYDROCHLORIC ACID SALTS**

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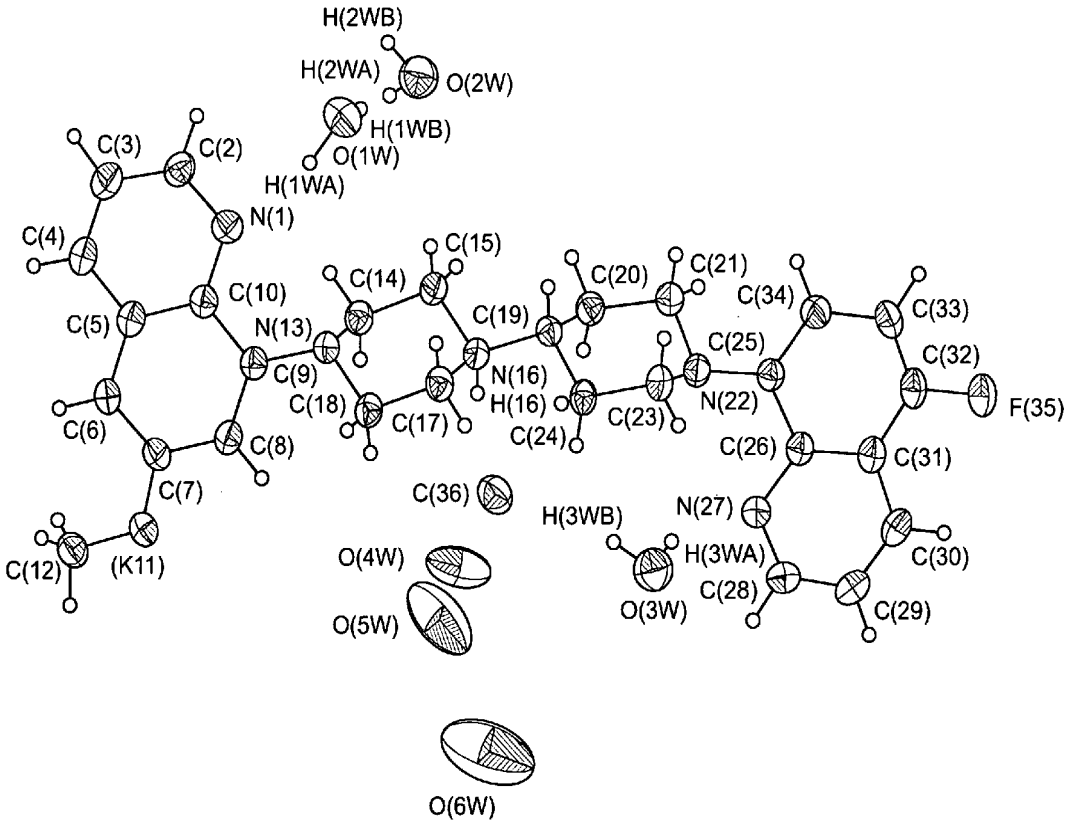
(57) **ABSTRACT**

The present invention relates to hydrochloric acid salt and crystalline forms of the 5-HT_{1A} binding agent 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline, as well as pharmaceutical compositions thereof, and methods of use thereof.



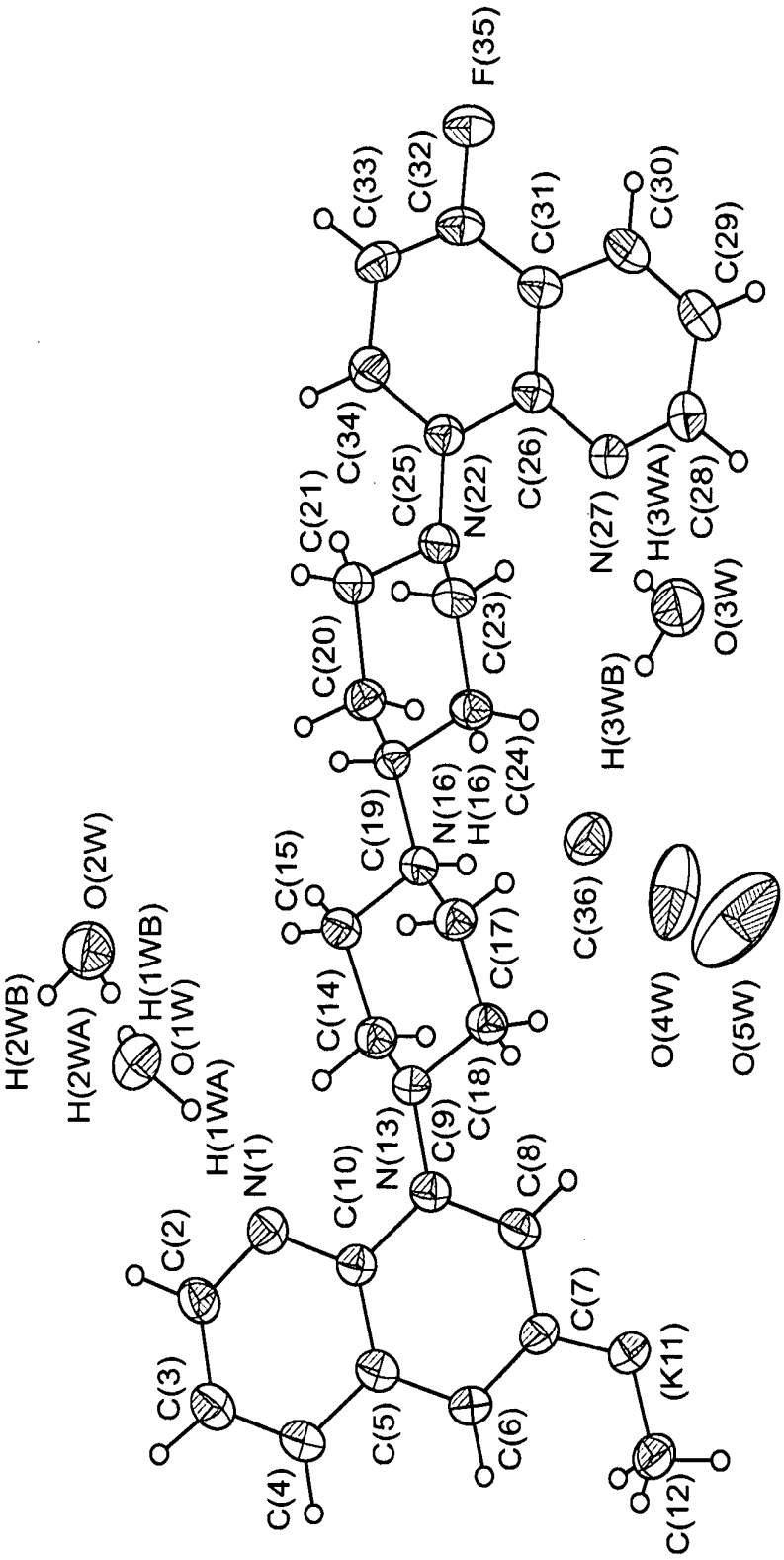

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FIG. 1

6-METHOXY-8-[4-(1-(5-FLUORO)-QUINOLIN-8-YL-PIPERIDIN-4-YL)-PIPERAZIN-1-YL]-QUINOLINE HYDROCHLORIC ACID SALTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent App. Ser. No. 60/812,168, filed Jun. 9, 2006, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to a hydrochloride salt of the 5-HT_{1A} binding agent 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline, as well as a crystalline form thereof, pharmaceutical compositions thereof, and methods of use thereof.

BACKGROUND OF THE INVENTION

[0003] N-Aryl-piperazine derivatives are known to bind to 5-HT_{1A} receptors and are useful as pharmaceutical agents for the treatment of various central nervous system (CNS) disorders such as cognitive disorders, anxiety disorders, and depression. See, e.g., Childers, et al., *J. Med. Chem.,* 2005, 48, 3467; and U.S. Pat. Nos. 6,465,482; 6,127,357; 6,469,007; and 6,586,436, as well as WO 97/03982. Among these, certain N-aryl-piperazine-piperidine compounds, including 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline (see Formula I), which is described in WO 2006/135839 have been found to modulate activity of the 5-HT_{1A} receptor and are useful, for example, for enhancing cognition, treating anxiety, and treating depression, among other CNS disorders.

[0004] Drug compounds are typically combined with other pharmaceutically acceptable ingredients to form compositions suitable for a desired mode of administration. Solid formulations often require that the drug compound have workable solid state characteristics such as stability to heat and humidity, ease of handling, and other characteristics that facilitate preparation of solid dosage forms. At the same time, good water solubility, which often translates to good bioavailability, is also desired. Accordingly, there is an ongoing need for stabler and more soluble solid forms of existing drug molecules. The salt and crystalline forms of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline described herein are directed toward this end.

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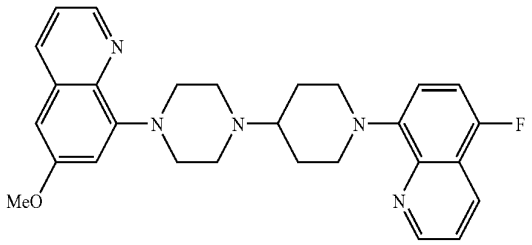

SUMMARY OF THE INVENTION

[0005] The present invention provides, inter alia, hydrochloric acid salts of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline.

[0006] The present invention further provides a crystalline form of a monohydrochloric acid salt of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline.

[0007] The present invention further provides methods of preparing the hydrochloric acid salts or crystalline form described herein.

[0008] The present invention further provides compositions comprising the hydrochloric acid salts or crystalline form described herein.

[0009] The present invention further provides methods of treating 5-HT_{1A} associated diseases by administering to a patient a therapeutically effective amount of a salt or crystalline form described herein, or composition thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. **1** depicts probability ellipsoids for 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride hexahydrate as determined by single crystal X-ray crystallography.

DETAILED DESCRIPTION

[0011] The present invention provides, inter alia, hydrochloric acid salts, including the mono-hydrochloric acid salt, of the compound 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline (see Formula I above) which can modulate the 5-HT_{1A} receptor and is useful in the treatment of CNS disorders. The salts of the invention can be crystalline, amorphous, or a combination thereof. In some embodiments, the salt is a monohydrochloric acid salt or tris(hydrochloric acid) salt. In further embodiments, the hydrochloric acid salt is hydrated, such as a dihydrate or hexahydrate. In further embodiments, crystalline monohydrochloride salt is characterized as having a particular crystalline form, such as described herein.

[0012] The phrase "hydrochloric acid salt of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline" or "hydrochloric acid salt of the invention" is meant to refer to any HCl salt of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline free base including mono-, bis-, tris- and other salts. The phrase is also meant to include hydrates of any of the salts including, for example, semi-, mono-, di-, tri-, tetra-, hexa- and other hydrates. Methods for determining acid and water/solvent content of salts are routine in the art and include, for example, elemental analysis, NMR, single crystal X-ray crystallography, electrochemical techniques, thermogravimetric analysis (TGA), and the like.

[0013] Hydrochloric acid salts of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline possess numerous advantages over the free base form. For example, the free base has relatively poor solubility in aqueous media (about 0.4 μg/mL) even in the presence of surfactants, indicating potential poor bioavailability. In contrast, a hydrochloride salt is more soluble in water than the free base, and has improved bioavailability over the free base. Other advantages of a hydrochloride salt include its crystallinity which aids in preparation of substantially pure API and facilitates handling. Hydrated hydrochloric acid salts are also advantageous in that their preparation would

not require rigorously anhydrous conditions for their preparation thereby greatly facilitating large scale production.

[0014] Methods of preparing the salts of the invention include any of a variety of techniques routine in the art. For example, free base 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline can be combined in solution with hydrochloric acid and the salt is then precipitated out. The relative amounts of free base and acid can vary depending on the desired salt. For example, the molar ratio of free base to acid can be about 1:1 in order to prepare a monohydrochloric acid salt, about 1:2 for a bis(hydrochloric acid) salt, or about 1:3 for a tris(hydrochloric acid) salt. As the salt is typically more soluble in polar solvents such as water than the free base, the free base and hydrochloric acid can be combined in a weakly polar or non-polar solvent system such that the newly formed salt readily precipitates out of solution. Optionally, antisolvent can be added to the solution containing the salt to induce precipitation. In some embodiments, the free base and hydrochloric acid are combined in a solvent system containing an alcohol such as methanol. In further embodiments, the salt is precipitated by addition of antisolvent such as an ether. Where hydrated salts are desired, water can be added to or made part of the solution prior to or during salt formation.

[0015] In a further aspect of the invention, a crystalline form of the monohydrochloric acid salt of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline is provided which is characterized by having a monoclinic space group. In some embodiments, the monoclinic space group is P2(1)/c (No. 14). In further embodiments, the crystalline form has unit cell parameters as follows: a=14.4 Å; b=7.6 Å; c=28.6 Å; and beta=107.1°. In further embodiments, the monohydrochloric acid salt having the above space group and unit cell is a hydrate, such as a hexahydrate. In yet further embodiments, the crystalline form has atomic coordinates substantially as provided in Table 2 and/or bond lengths and bond angles substantially as provided in Tables 3 and 4. A description of the characterization of this crystalline form is provided in the Examples.

[0016] Methods of preparing the crystalline form of the invention include precipitating 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride from an aqueous solution. In some embodiments, the aqueous solution can contain organic solvents such as an alcohol (e.g., ethanol). For example, the volume ratio of water to alcohol can be about 1:1 to about 1:10, about 1:1 to about 1:5, about 1:1 to about 1:4, or about 1:3. Precipitation can be carried out by any suitable means including reducing the temperature of the solution, reducing volume of the solution (e.g., by evaporation), addition of antisolvent (e.g., directly, by vapor diffusion, or by layer diffusion), or any combination thereof. After isolation, the precipitated crystalline form can be subject to drying to remove residual solvent(s). In some embodiments, the precipitated crystalline form is subject to drying in vacuo at moderately elevated temperature such as from about 30 to about 55° C., about 35 to about 50° C., about 40 to about 50° C., or about 45° C.

Compositions

[0017] The present invention further provides compositions containing a hydrochloric acid salt or crystalline form of the invention and one or more other ingredients. In some embodiments, the composition contains at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98.0%, at least about 98.1%, at least about 98.2%, at least about 98.3%, at least about 98.4%, at least about 98.5%, at least about 98.6%, at least about 98.7%, at least about 98.8%, at least about 98.9%, at least about 99.0%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8%, or at least about 99.9% by weight of a hydrochloric acid salt 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline. In some embodiments, the salt is a monohydrochloric acid salt or a tris(hydrochloric acid) salt.

[0018] In some embodiments, the composition contains at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98.0%, at least about 98.1%, at least about 98.2%, at least about 98.3%, at least about 98.4%, at least about 98.5%, at least about 98.6%, at least about 98.7%, at least about 98.8%, at least about 98.9%, at least about 99.0%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8%, or at least about 99.9% by weight of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride, having a crystalline form characterized by monoclinic space group P2(1)/c (No. 14) having unit cell parameters: a=14.4 Å; b=7.6 Å; c=28.6 Å; and beta=107.1°. In further embodiments, the monohydrochloric acid salt having the above space group and unit cell is a hydrate, such as a hexahydrate.

[0019] In some embodiments, the composition is a pharmaceutical composition which contains at least one salt or crystalline form of the invention and at least one pharmaceutically acceptable carrier. In further embodiments, the composition is a pharmaceutical composition which contains at least one active pharmaceutical ingredient which is 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride or tris(hydrochloride), or hydrate thereof, and at least one pharmaceutically acceptable carrier. In further embodiments, the composition is a pharmaceutical composition which contains at least one active pharmaceutical ingredient which is 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride hexahydrate or tris(hydrochloride) dihydrate, and at least one pharmaceutically acceptable carrier. In further embodiments, the composition is a pharmaceutical composition which contains at least one active pharmaceutical ingredient which is 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride hexahydrate having the crystalline form described herein and at least one pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is suitable for oral administration. In some embodiments, the composition is provided in the form of a sustained release dosage form.

[0020] Pharmaceutically acceptable excipients (carriers) can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The excipients can be saline, gum acacia, gelatin, starch

paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment the excipients are sterile when administered to an animal. The excipient should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms. Water is a particularly useful excipient when the compound or a pharmaceutically acceptable salt of the compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0021] Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups, and elixirs. The salts and crystalline forms of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives including solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmoregulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, including sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

[0022] The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule. Other examples of suitable excipients are described in Remington's Pharmaceutical Sciences 1447 1676 (Alfonso R. Gennaro, ed., 19th ed. 1995).

[0023] In one embodiment, the salts and crystalline forms of the invention are formulated in accordance with routine procedures as a composition adapted for oral administration to humans. Compositions for oral delivery can be in the form of tablets, lozenges, buccal forms, troches, aqueous or oily suspensions or solutions, granules, powders, emulsions, capsules, syrups, or elixirs for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. In powders, the carrier can be a finely divided solid, which is an admixture with the finely divided compound or pharmaceutically acceptable salt of the compound. In tablets, the compound or pharmaceutically acceptable salt of the compound is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets can contain up to about 99% of the salt or crystalline form.

[0024] Capsules may contain mixtures of the compounds or pharmaceutically acceptable salts of the compounds with inert fillers and/or diluents such as pharmaceutically acceptable starches (e.g., corn, potato, or tapioca starch), sugars, artificial sweetening agents, powdered celluloses (such as crystalline and microcrystalline celluloses), flours, gelatins, gums, etc.

[0025] Tablet formulations can be made by conventional compression, wet granulation, or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents (including, but not limited to, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidine, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, low melting waxes, and ion exchange resins.) Surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine.

[0026] When in a tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound or a pharmaceutically acceptable salt of the compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule can be imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

[0027] In another embodiment, the salts and crystalline forms can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site

of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the salts and crystalline forms are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the salts and crystalline forms are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[0028] In another embodiment, the salts and crystalline forms can be administered transdermally through the use of a transdermal patch. Transdermal administrations include administrations across the surface of the body and the inner linings of the bodily passages including epithelial and mucosal tissues. Such administrations can be carried out using the present salts and crystalline forms in lotions, creams, foams, patches, suspensions, solutions, and suppositories (e.g., rectal or vaginal).

[0029] Transdermal administration can be accomplished through the use of a transdermal patch containing the salt or crystalline form of the invention and a carrier that is inert to the compound or pharmaceutically acceptable salt of the compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams or ointments, pastes, gels, or occlusive devices. The creams or ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the compound or pharmaceutically acceptable salt of the compound into the blood stream, such as a semi-permeable membrane covering a reservoir containing the compound or pharmaceutically acceptable salt of the compound with or without a carrier, or a matrix containing the active ingredient.

[0030] The salts and crystalline forms of the invention may be administered rectally or vaginally in the form of a conventional suppository. Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water-soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

[0031] The salts and crystalline forms can be administered by controlled-release or sustained-release means or by delivery devices that are known to those of ordinary skill in the art. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those skilled in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

[0032] In one embodiment a controlled- or sustained-release composition comprises a minimal amount of the salt or crystalline form to treat or prevent a 5-HT_{1A}-related disorder in a minimal amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased compliance by the animal being treated. In addition, controlled or sustained release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the compound or a pharmaceutically acceptable salt of the compound, and can thus reduce the occurrence of adverse side effects.

[0033] Controlled- or sustained-release compositions can initially release an amount of the compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the compound this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the compound or a pharmaceutically acceptable salt of the compound in the body, the compound or a pharmaceutically acceptable salt of the compound can be released from the dosage form at a rate that will replace the amount of the compound or a pharmaceutically acceptable salt of the compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

[0034] The amount of the salt or crystalline form delivered is an amount that is effective for treating or preventing a 5-HT_{1A}-related disorder. In addition, in vitro or in vivo assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed can also depend on the route of administration, the condition, the seriousness of the condition being treated, as well as various physical factors related to the individual being treated, and can be decided according to the judgment of a health-care practitioner. Equivalent dosages may be administered over various time periods including, but not limited to, about every 2 hours, about every 6 hours, about every 8 hours, about every 12 hours, about every 24 hours, about every 36 hours, about every 48 hours, about every 72 hours, about every week, about every two weeks, about every three weeks, about every month, and about every two months. The number and frequency of dosages corresponding to a completed course of therapy will be determined according to the judgment of a health-care practitioner. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one compound is administered, the effective dosage amounts correspond to the total amount administered.

[0035] The amount of the salt or crystalline form that is effective for treating or preventing a 5-HT_{1A}-related disorder will typically range from about 0.001 mg/kg to about 600 mg/kg of body weight per day, in one embodiment, from about 1 mg/kg to about 600 mg/kg body weight per day, in another embodiment, from about 10 mg/kg to about 400 mg/kg body weight per day, in another embodiment, from

about 10 mg/kg to about 200 mg/kg of body weight per day, in another embodiment, from about 10 mg/kg to about 100 mg/kg of body weight per day, in another embodiment, from about 1 mg/kg to about 10 mg/kg body weight per day, in another embodiment, from about 0.001 mg/kg to about 100 mg/kg of body weight per day, in another embodiment, from about 0.001 mg/kg to about 10 mg/kg of body weight per day, and in another embodiment, from about 0.001 mg/kg to about 1 mg/kg of body weight per day.

[0036] In one embodiment, the pharmaceutical composition is in unit dosage form, e.g., as a tablet, capsule, powder, solution, suspension, emulsion, granule, or suppository. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. Such unit dosage form may contain from about 0.01 mg/kg to about 250 mg/kg, and may be given in a single dose or in two or more divided doses. Variations in the dosage will necessarily occur depending upon the species, weight and condition of the patient being treated and the patient's individual response to the medicament.

[0037] In one embodiment, the unit dosage form is about 0.01 to about 1000 mg. In another embodiment, the unit dosage form is about 0.01 to about 500 mg; in another embodiment, the unit dosage form is about 0.01 to about 250 mg; in another embodiment, the unit dosage form is about 0.01 to about 100 mg; in another embodiment, the unit dosage form is about 0.01 to about 50 mg; in another embodiment, the unit dosage form is about 0.01 to about 25 mg; in another embodiment, the unit dosage form is about 0.01 to about 10 mg; in another embodiment, the unit dosage form is about 0.01 to about 5 mg; and in another embodiment, the unit dosage form is about 0.01 to about 10 mg.

[0038] In some embodiments, the composition is suitable for oral administration and/or comprises an oral dosage form.

[0039] The salts and crystalline forms can be assayed in vitro or in vivo for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

[0040] Pharmaceutical compositions can be prepared in accordance with acceptable pharmaceutical procedures, such as, for example, those described in *Remingtons Pharmaceutical Sciences,* 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, Pa. (1985), which is incorporated herein by reference in its entirety. Pharmaceutically acceptable carriers are those carriers that are compatible with the other ingredients in the formulation and are biologically acceptable.

Pharmaceutical Methods

[0041] The salts and crystalline forms of the invention are 5-HT_{1A} modulators which are useful in methods of treating various 5-HT_{1A}-related diseases or disorders such as cognition-related disorders or anxiety-related disorder.

[0042] Cognitive-related disorders can include improving cognitive function or inhibiting cognitive deficits. Examples of improvements in cognitive function include, without limitation, memory improvement and retention of learned information. Accordingly, the compounds are useful for slowing the loss of memory and cognition and for maintaining independent function for patients afflicted with a cognition-related disorder. Accordingly, the salts and crystalline forms of the present invention are useful for improving cognitive function. Further examples of cognition-related disorders include dementia, Parkinson's disease, Huntington's disease, Alzheimer's disease, cognitive deficits associated with Alzheimer's disease, mild cognitive impairment, and schizophrenia.

[0043] Example of anxiety-related disorders include attention deficit disorder, obsessive compulsive disorder, substance addiction, withdrawal from substance addiction, premenstrual dysphoric disorder, social anxiety disorder, anorexia nervosa, and bulimia nervosa.

[0044] The salts and crystalline forms of the invention are further useful for treating Alzheimer's disease. In some embodiments, the method for treating Alzheimer's disease includes administering a second therapeutic agent. In some embodiments, the second therapeutic agent is an anti-depressant agent, an anti-anxiety agent, an anti-psychotic agent, or a cognitive enhancer.

[0045] The salts and crystalline forms of the invention are further useful for treating mild cognitive impairment (MCI). In some embodiments, the method for treating MCI includes administering a second therapeutic agent. In some embodiments, the second therapeutic agent is an anti-depressant agent, an anti-anxiety agent, an anti-psychotic agent, or a cognitive enhancer.

[0046] The salts and crystalline forms of the invention are further useful for treating depression. In some embodiments, the method for treating depression includes administering a second therapeutic agent. In some embodiments, the second therapeutic agent is an anti-depressant agent, an anti-anxiety agent, an anti-psychotic agent, or a cognitive enhancer.

[0047] The salts and crystalline forms of the invention are further useful for treating sexual dysfunction, such as sexual dysfunction associated with drug treatment (e.g., with an antidepressant, an antipsychotic, or an anticonvulsant).

[0048] In certain embodiments, the drug treatment associated with sexual dysfunction involves a selective serotonin reuptake inhibitor (SSRI) (for example, fluoxetine, citalopram, escitalopram oxalate, fluvoxamine maleate, paroxetine, or sertraline), a tricyclic antidepressant (for example, desipramine, amitriptyline, amoxipine, clomipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, dothiepin, butriptyline, iprindole, or lofepramine), an aminoketone class compound (for example, bupropion). In some embodiments, the drug is a monoamine oxidase inhibitor (MAOI) (for example, phenelzine, isocarboxazid, or tranylcypromine), a serotonin and norepinepherine reuptake inhibitor (SNRI) (for example, venlafaxine, nefazodone, milnacipran, duloxetine), a norepinephrine reuptake inhibitor (NRI) (for example, reboxetine), a partial 5-HT1A agonist (for example, buspirone), a 5-HT2A receptor antagonist (for example, nefazodone), a typical antipsychotic drug, or an atypical antipsychotic drug. Examples of such antipsychotic drugs include aliphatic phethiazine, a piperazine phenothiazine, a butyrophenone, a substituted benzamide,

and a thioxanthine. Additional examples of such drugs include haloperidol, olanzapine, clozapine, risperidone, pimozide, aripiprazol, and ziprasidone. In some cases, the drug is an anticonvulsant, e.g., phenobarbital, phenyloin, primidone, or carbamazepine. In some cases, the patient in need of treatment for sexual dysfunction is being treated with at least two drugs that are antidepressant drugs, antipsychotic drugs, anticonvulsant drugs, or a combination thereof.

[0049] In some embodiments of the invention, the sexual dysfunction comprises a deficiency in penile erection.

[0050] In some embodiments, the salts or crystalline forms are effective for ameliorating sexual dysfunction in an animal model of sexual dysfunction associated with drug treatment, for example, in an animal model of sexual dysfunction that is an antidepressant drug-induced model of sexual dysfunction.

[0051] The salts and crystalline forms of the invention are further useful for improving sexual function in a patient.

[0052] As used herein, the term "patient" refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. In some embodiments, the patient is in need of treatment.

[0053] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

[0054] (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

[0055] (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting or slowing further development of the pathology and/or symptomatology); and

[0056] (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Administration, Compositions, and Dosage Forms

[0057] The salts and crystalline forms of the invention can be administered neat or as a component of a composition that comprises a physiologically acceptable carrier or vehicle. A pharmaceutical composition of the invention can be prepared using a method comprising admixing the compound or a pharmaceutically acceptable salt of the compound and a physiologically acceptable carrier, excipient, or diluent. Admixing can be accomplished using methods well known for admixing a compound or a pharmaceutically acceptable salt of the compound and a physiologically acceptable carrier, excipient, or diluent.

[0058] The present pharmaceutical compositions can be administered orally. The salts and crystalline forms of the invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral, rectal, vaginal, and intestinal mucosa, etc.) and can be administered together with another therapeutic agent. Administration can be systemic or local. Various known delivery systems, including encapsulation in liposomes, microparticles, microcapsules, and capsules, can be used.

[0059] Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. In some instances, administration will result of release of the compound or a pharmaceutically acceptable salt of the compound into the bloodstream. The mode of administration is left to the discretion of the practitioner.

[0060] In one embodiment, the salts and crystalline forms of the invention are administered orally.

[0061] In another embodiment, the salts and crystalline forms of the invention are administered intravenously.

[0062] In another embodiment, it may be desirable to administer the salts and crystalline forms of the invention locally. This can be achieved, for example, by local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or edema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

[0063] In certain embodiments, it can be desirable to introduce the salts and crystalline forms of the invention into the central nervous system, circulatory system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal injection, paraspinal injection, epidural injection, enema, and by injection adjacent to the peripheral nerve. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

[0064] Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the salts and crystalline forms can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

[0065] In another embodiment, the salts and crystalline forms of the invention can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990) and Treat et al., Liposomes in the Therapy of Infectious Disease and Cancer 317-327 and 353-365 (1989)).

[0066] In yet another embodiment, the salts and crystalline forms of the invention can be delivered in a controlled-release system or sustained-release system (see, e.g., Goodson, in Medical Applications of Controlled Release, vol. 2, pp. 115 138 (1984)). Other controlled or sustained-release systems discussed in the review by Langer, Science

249:1527 1533 (1990) can be used. In one embodiment, a pump can be used (Langer, Science 249:1527-1533 (1990); Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); and Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release (Langer and Wise eds., 1974); Controlled Drug Bioavailability, Drug Product Design and Performance (Smolen and Ball eds., 1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 2:61 (1983); Levy et al., Science 228:190 (1935); During et al., Ann. Neural. 25:351 (1989); and Howard et al., J. Neurosurg. 71:105 (1989)).

Combination Therapy

[0067] The salts and crystalline forms of the invention can be administered to a patient in combination with a therapeutically effective amount of one or more further therapeutic agents. Effective amounts of further therapeutic agents are well known to those skilled in the art. It is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective amount range. The salt or crystalline form and the other therapeutic agent can act additively or, in one embodiment, synergistically. In one embodiment of the invention, where another therapeutic agent is administered to an animal, the effective amount of salt or crystalline form is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the salt or crystalline form and the other therapeutic agent can act synergistically. In some cases, the patient in need of treatment is being treated with one or more other therapeutic agents. In some cases, the patient in need of treatment is being treated with at least two other therapeutic agents.

[0068] In one embodiment, the other therapeutic agent is selected from one or more of the following: anti-depressant agents, anti-anxiety agents, anti-psychotic agents, or cognitive enhancers. Examples of classes of antidepressants that can be used in combination with the active compounds of this invention include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), NK-1 receptor antagonists, monoamine oxidase inhibitors (MAOs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, and atypical antidepressants. Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable tertiary amine tricyclics and secondary amine tricyclics include amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dothiepin, butriptyline, iprindole, lofepramine, nortriptyline, protriptyline, amoxapine, desipramine and maprotiline. Suitable selective serotonin reuptake inhibitors include fluoxetine, citolopram, escitalopram, fluvoxamine, paroxetine and sertraline. Examples of monoamine oxidase inhibitors include isocarboxazid, phenelzine, and tranylcypromine. Suitable reversible inhibitors of monoamine oxidase include moclobemide. Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include venlafaxine, nefazodone, milnacipran, and duloxetine. Suitable CRF antagonists include those compounds described in International Patent Publication Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677. Suitable atypical anti-depressants include bupropion, lithium, nefazodone, trazodone and viloxazine. Suitable NK-1 receptor antagonists include those referred to in International Patent Publication WO 01/77100.

[0069] Anti-anxiety agents that can be used in combination with the active compounds of this invention include without limitation benzodiazepines and serotonin 1A ($5\text{-}HT_{1A}$) agonists or antagonists, especially $5\text{-}HT_{1A}$ partial agonists, and corticotropin releasing factor (CRF) antagonists. Exemplary suitable benzodiazepines include alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam. Exemplary suitable $5\text{-}HT_{1A}$ receptor agonists or antagonists include buspirone, flesinoxan, gepirone and ipsapirone.

[0070] Anti-psychotic agents that can be used in combination with the active compounds of this invention include without limitation aliphatic phethiazine, a piperazine phenothiazine, a butyrophenone, a substituted benzamide, and a thioxanthine. Additional examples of such drugs include without limitation haloperidol, olanzapine, clozapine, risperidone, pimozide, aripiprazol, and ziprasidone. In some cases, the drug is an anticonvulsant, e.g., phenobarbital, phenyloin, primidone, or carbamazepine.

[0071] Cognitive enhancers that can be used in combination with the active compounds of this invention include, without limitation, drugs that modulate neurotransmitter levels (e.g., acetylcholinesterase or cholinesterase inhibitors, cholinergic receptor agonists or serotonin receptor antagonists), drugs that modulate the level of soluble Aβ, amyloid fibril formation, or amyloid plaque burden (e.g., γ-secretase inhibitors, β-secretase inhibitors, antibody therapies, and degradative enzymes), and drugs that protect neuronal integrity (e.g., antioxidants, kinase inhibitors, caspase inhibitors, and hormones). Other representative candidate drugs that are co-administered with the compounds of the invention include cholinesterase inhibitors, (e.g., tacrine (COGNEX®), donepezil (ARICEPT®), rivastigmine (EXELON®) galantamine (REMINYL®), metrifonate, physostigmine, and Huperzine A), N-methyl-D-aspartate (NMDA) antagonists and agonists (e.g., dextromethorphan, memantine, dizocilpine maleate (MK-801), xenon, remacemide, eliprodil, amantadine, D-cycloserine, felbamate, ifenprodil, CP-101606 (Pfizer), Delucemine, and compounds described in U.S. Pat. Nos. 6,821,985 and 6,635,270), ampakines (e.g., cyclothiazide, aniracetam, CX-516 (Ampalex®), CX-717, CX-516, CX-614, and CX-691 (Cortex Pharmaceuticals, Inc. Irvine, Calif.), 7-chloro-3-methyl-3-4-dihydro-2H-1,2,4-benzothiadiazine S,S-dioxide (see Zivkovic et al., 1995, *J. Pharmacol. Exp. Therap.*, 272:300-309; Thompson et al., 1995, *Proc. Natl. Acad. Sci. USA*, 92:7667-7671), 3-bicyclo[2,2,1]hept-5-en-2-yl-6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (Yamada, et al., 1993, *J. Neurosc.* 13:3904-3915); 7-fluoro-3-methyl-5-ethyl-1,2,4-benzothiadiazine-S,S-dioxide; and compounds described in U.S. Pat. No. 6,620,808 and International Patent Application Nos. WO 94/02475, WO 96/38414, WO 97/36907, WO 99/51240, and WO 99/42456), benzodiazepine (BZD)/GABA receptor complex modulators (e.g., progabide, gengabine, zaleplon, and compounds described in U.S. Pat. Nos. 5,538,956, 5,260,331, and 5,422,355); serotonin antagonists (e.g., 5HT receptor modulators, $5HT_{1A}$ antagonists or agonists (including without limitation lecozotan and compounds described in U.S.

Pat. Nos. 6,465,482, 6,127,357, 6,469,007, and 6,586,436, and in PCT Publication No. WO 97/03982) and 5-HT_6 antagonists (including without limitation compounds described in U.S. Pat. Nos. 6,727,236, 6,825,212, 6,995,176, and 7,041,695)); nicotinics (e.g., niacin); muscarinics (e.g., xanomeline, CDD-0102, cevimeline, talsaclidine, oxybutin, tolterodine, propiverine, tropsium chloride and darifenacin); monoamine oxidase type B (MAO B) inhibitors (e.g., rasagiline, selegiline, deprenyl, lazabemide, safinamide, clorgyline, pargyline, N-(2-aminoethyl)-4-chlorobenzamide hydrochloride, and N-(2-aminoethyl)-5(3-fluorophenyl)-4-thiazolecarboxamide hydrochloride); phosphodiesterase (PDE) IV inhibitors (e.g., roflumilast, arofylline, cilomilast, rolipram, RO-20-1724, theophylline, denbufylline, ARIFLO, ROFLUMILAST, CDP-840 (a tri-aryl ethane) CP80633 (a pyrimidone), RP 73401 (Rhone-Poulenc Rorer), denbufylline (SmithKline Beecham), arofylline (Almirall), CP-77,059 (Pfizer), pyrid[2,3d]pyridazin-5-ones (Syntex), EP-685479 (Bayer), T-440 (Tanabe Seiyaku), and SDZ-ISQ-844 (Novartis)); G proteins; channel modulators; immunotherapeutics (e.g., compounds described in U.S. Patent Application Publication No. US 2005/0197356 and US 2005/0197379); anti-amyloid or amyloid lowering agents (e.g., bapineuzumab and compounds described in U.S. Pat. No. 6,878,742 or U.S. Patent Application Publication Nos. US 2005/0282825 or US 2005/0282826); statins and peroxisome proliferators activated receptor (PPARS) modulators (e.g., gemfibrozil (LOPID®), fenofibrate (TRICOR®), rosiglitazone maleate (AVANDIA®), pioglitazone (Actos™), rosiglitazone (Avandia™), clofibrate and bezafibrate); cysteinyl protease inhibitors; an inhibitor of receptor for advanced glycation endproduct (RAGE) (e.g., aminoguanidine, pyridoxaminem carnosine, phenazinediamine, OPB-9195, and tenilsetam); direct or indirect neurotropic agents (e.g., Cerebrolysin®, piracetam, oxiracetam, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454)); beta-secretase (BACE) inhibitors, α-secretase, immunophilins, caspase-3 inhibitors, Src kinase inhibitors, tissue plasminogen activator (TPA) activators, AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) modulators, M4 agonists, JNK3 inhibitors, LXR agonists, H3 antagonists, and angiotensin IV antagonists. Other cognition enhancers include, without limitation, acetyl-1-carnitine, citicholine, huperzine, DMAE (dimethylaminoethanol), Bacopa monneiri extract, Sage extract, L-alpha glyceryl phosphoryl choline, Ginko biloba and Ginko biloba extract, Vinpocetine, DHA, nootropics including Phenyltropin, Pikatropin (from Creative Compounds, LLC, Scott City, Mo.), besipirdine, linopirdine, sibopirdine, estrogen and estrogenic compounds, idebenone, T-588 (Toyama Chemical, Japan), and FK960 (Fujisawa Pharmaceutical Co. Ltd.). Compounds described in U.S. Pat. Nos. 5,219,857, 4,904,658, 4,624,954 and 4,665,183 are also useful as cognitive enhancers as described herein. Cognitive enhancers that act through one or more of the above mechanisms are also within the scope of this invention.

[0072] In one embodiment, the salt or crystalline form of the invention and cognitive enhancer act additively or, in one embodiment, synergistically. In one embodiment, where a cognitive enhancer and a salt or crystalline form of the invention are co-administered to an animal, the effective amount of the salt or crystalline form of the invention is less than its effective amount would be where the cognitive enhancer agent is not administered. In one embodiment, where a cognitive enhancer and a salt or crystalline form of the invention are co-administered to an animal, the effective amount of the cognitive enhancer is less than its effective amount would be where the salt or crystalline form of the invention is not administered. In one embodiment, a cognitive enhancer and a salt or crystalline form of the invention are co-administered to an animal in doses that are less than their effective amounts would be where they were no co-administered. In these cases, without being bound by theory, it is believed that the compound or a pharmaceutically acceptable salt of the compound and the cognitive enhancer act synergistically.

[0073] In one embodiment, the other therapeutic agent is an agent useful for treating Alzheimer's disease or conditions associate with Alzheimer's disease, such as dementia. Exemplary agents useful for treating Alzheimer's disease include, without limitation, donepezil, rivastigmine, galantamine, memantine, and tacrine.

[0074] In one embodiment, the salt or crystalline form is administered concurrently with at least one further therapeutic agent.

[0075] In one embodiment, a composition comprising an effective amount of the salt or crystalline form and an effective amount of at least one further therapeutic agent within the same composition can be administered.

[0076] In another embodiment, a composition comprising an effective amount of the salt or crystalline form and a separate composition comprising an effective amount of a further therapeutic agent can be concurrently administered. In another embodiment, an effective amount of the salt or crystalline form is administered prior to or subsequent to administration of an effective amount of a further therapeutic agent. In this embodiment, the salt or crystalline form is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the salt or crystalline form exerts its preventative or therapeutic effect for treating or preventing a 5-HT_{1A}-related disorder.

[0077] In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

EXAMPLES

Example 1

Preparation of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline (free base)

Step 1: 6-Methoxy-8-(1-piperazinyl)quinoline

[0078] A mixture of 8-amino-6-methoxyquinoline (150.0 g, 0.862 mol) and bis(2-chloroethyl)amine (219 g, 1.23 mol) in 6 parts (volume of hexanol v. weight of 8-amino-6-methoxyquinoline) of 1-hexanol (900 mL) was heated to 145° C. and stirred for 21 hours. Upon completion, the reaction mixture was cooled to 50-60° C. and 507 g of aqueous NaOH solution was added slowly. The reaction mixture was cooled to 25-30° C. and isopropyl acetate (750 mL) was added. The mixture was clarified through a Celite

pad. The aqueous phase was then split off. The organic solution was treated with a slurry of adipic acid (126 g, 0.862 mol) in isopropyl acetate (250 mL). The resulting mixture was stirred for 16 hours to form 6-methoxy-8-(1-piperazinyl)quinoline adipate salt. The adipate salt was filtered and washed with isopropyl acetate (2×150 mL) and dried by nitrogen flow to give adipate of 6-methoxy-8-piperazin-1-yl-quinoline (186 g, 55% yield) with ~97% HPLC area, 88% strength purity in 51% yield.

[0079] For purification of the salt, 580 g of the crude adipate salt and 2.8 L of methanol were mixed and heated to 65° C. and a dark solution was obtained. To this solution was charged slowly 1.1 liter of isopropyl acetate over 40 min at about 63° C. The mixture was stirred at about 63° C. for about 1 h and cooled to 0-5° C. After stirring at 0-5° C. for 2 hours, the mixture was filtered and washed with 300 mL of isopropyl acetate and dried with airflow. Yield, 395 g, 68.1% recovery yield.

[0080] To liberate 6-methoxy-8-(1-piperazinyl)quinoline from its adipate salt, 100 g (0.257 mol) of the adipate salt was added into a 2-L reactor followed by the addition of 500 mL of dichloromethane. To this mixture was added 100 g of water followed by the slow (in about 15 min) addition of 41 g of 50% sodium hydroxide solution to maintain the pH in the 13-14 range, adding sodium hydroxide solution as necessary if the pH is below 10. The organic bottom layer was separated and filtered through a pad of activated basic aluminum oxide (100 g, 6.5 cm diameter×3 cm depth). The pad was washed with 100 mL of isopropyl acetate twice. The dichloromethane was replaced by toluene by distillation under vacuum (450 to 500 mm Hg) while 3×150 mL of toluene was added into the reactor until the final volume was about 135 mL. Some white solid precipitated after distillation, the solid was removed by filtration, the filter cake was washed with 50 mL of toluene. Final volume, 185 mL, purity 97.56%, solution strength 27.4%).

Step 2: 8-Bromo-5-fluoroquinoline

[0081] A 2-L reactor equipped with a mechanic agitator, a condenser, a thermocouple, a baffle, and nitrogen inlet was charged with 228 g of water, 200 g of 2-bromo-5-fluoroaniline and 80 g of 4-nitrophenol. To this mixture was charged 96% sulfuric acid in 10-30 min at 20-120° C. The mixture was heated to 135-140° C. and 194 g of glycerol was charged into the reactor over two hours at 135-145° C. The mixture was held at 135-145° C. for 1 hour after the addition. The reaction mixture was cooled to below 20-50° C. and slowly transferred to a 5-L reactor containing 1100 g of water and 1210 g of toluene. The 2-L reactor was washed with 300 g of water and the wash was combined into the 5-L reactor. The pH of the contents in the 5-L reactor was adjusted to pH 8-10 by adding approximately 1233 g (1370 mL) ammonium hydroxide (28-30% NH_3) at 20-40° C. The mixture was stirred at room temperature for 15 min and the solid by-product was filtered off while the filtrate was retained. The filter cake was washed with 400 mL of toluene and the all the filtrate was combined and charged a 3-L reactor. About 500 ml of 8.5% KOH solution was charged into the 3-L reactor and stirred for 10 min and bottom aqueous layer was spit off. A second portion of 500 ml of 8.5% KOH solution was added and the mixture was stirred for 15 min and the bottom aqueous layer was split off. Water 500 mL was added and stirred for 15 min before the bottom aqueous layer was split off. The organic layer was heated to distill off about 100-200 mL of toluene to azeotropically remove water. A clear solution was obtained. Yield: about 178 g 8-bromo-5-fluoroquinoline, ~75%.

[0082] Alternatively, 8-bromo-5-fluoroquinoline was prepared by adding a warm mixture containing 2-bromo-5-fluoroaniline (100 g, 1.0 eq), 4-nitrophenol (40 g, 0.54 eq), and glycerol (97 g, 2.0 eq) over 1.5 hours to sulfuric acid (267 mL) and water (114 mL) at 140-150° C. The initial mixture showed 37.8% 4-nitrophenol by relative HPLC area %. Samples showed 4.7% 4-nitrophenol immediately after adding 50% of mixed starting materials and 5.0% immediately after adding all of the materials. The yield upon workup was 87.5%, with total impurities 0.29%. Addition of less (0.46 eq, 34 g) 4-nitrophenol also successfully produced the intermediate of interest at acceptable yield.

Step 3: 1-(5-Fluoroquinolin-8-yl)piperidin-4-one

[0083] A 5-L jacketed cylindrical reactor equipped with an impeller-style agitator, condenser, thermocouple, and vacuum/nitrogen inlet was charged 2-L, 15% toluene solution of 8-bromo-5-fluoroquinoline, 209 g of 1,4-dioxa-8-azaspiro[4,5]decane. Meanwhile in a 500-mL Erlenmeyer flask, a suspension of 16.5 g (26.5 mmol)±-[1,1'-binaphthalene]-2,2'-diylbis[diphenyl-phosphine, and 6.08 g (6.64 mmol) tris[μ-[(1,2-η:4,5-η)-(1E,4E)-1,5-diphenyl-1,4-pentadien-3-one]]dipalladium in 260 g of toluene was prepared. This freshly made suspension was charged into the 5-L reactor followed by a rinse of 170 g of toluene. 166 g sodium tert-butoxide was then charged into the reactor followed by a rinse with 430 g of toluene. The reactor was degassed by vacuum to less than 125 mmHg and then filled with nitrogen to atmosphere three times. The mixture was then heated to 50-60° C. and stirred for 1 h and then heat to 65-75° and stirred at this temperature for about 10 hours. The mixture was cooled to 40-50° C. and then quenched with 800 g of water. The lower aqueous layer was split off and the volume of the organic layer was reduced to about 1.5 L by vacuum distillation. To this residual was charged 2.28 kg of 20% sulfuric acid at 25-30° C. The mixture was stirred for an hour and was clarified by filtration and a bi-phase filtrate was obtained. The aqueous phase was split and retained. Toluene 870 g was added to the aqueous solution and the mixture was neutralized by slowly adding 770 g 50% sodium hydroxide solution. The lower aqueous layer was split off and extracted with 600 g of toluene. The organic layers were combined and the volume of the reaction was reduced to about 1 L by vacuum distillation. The residue was cooled to room temperature and 480 g of toluene was charged. The mixture was heated to 45-55° C. to form a clear solution, which was filtered through a celite/charcoal pad to remove palladium. The filtrate was concentrated by vacuum distillation to about 0.7 L and diluted with 620 g heptane, cooled to −15 to −5° C. to form a slurry. The solid was collected by filtration. The product was dried by air flow at room temperature. Typical yield is about 70%.

Step 4: 6-Methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline

[0084] Toluene (118 g), sodium triacetoxyborohydride (44.5 g) were mixed at 0° C. to room temperature. To this mixture was charged a premixed toluene solution of 6-methoxy-8-(1-piperazinyl)quinoline (Step 1, 160 g, 27.4 wt % in

toluene) and 1-(5-fluoroquinolin-8-yl)piperidin-4-one (Step 3, 41 g). The resulting mixture was stirred for 2 to 3 hours at about 30° C. KOH solution (443 g 9% in water) was charged to quench the residual sodium triacetoxyborohydride. Heptane (118 g) was added to further precipitate the product. The product was then filtered and washed with ethanol (2×100 ml). Yield 68 g, 86%. This crude product (67 g) was dissolved in 586 g dichloromethane and passed through a charcoal/celite pad to remove palladium. The dichloromethane was distilled off while 400 g of ethanol was slowly added at the same time. The resulting slurry was filtered and washed with ethanol twice (65 g+100 g). The product was dried in oven at 55° C. overnight. Purification recovery yield 59.9 g, 89.4%.

Example 2

Preparation of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride

[0085] 6-Methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline (free base) (25 g, 53 mmol) was suspended in anhydrous methanol (150 mL) in a 3-neckflask equipped with a mechanical stirrer in an inert atmosphere. To the suspension was added in one portion 1N ethereal hydrochloric acid (53 mL, 53 mmol), which resulted in a clear solution. No exotherm was observed. The solution was treated with one portion of anhydrous diethyl ether (300 mL) which started a slow crystallization. The crystals were stirred at ambient temperature for 16 hrs. The larger sized crystals changed overnight to a fine crystalline suspension. The crystals were filtered with the exclusion of moisture (under N_2) and dried in a vacuum oven at 60° C. under a minute stream of nitrogen for 48 h. The crystalline solids (25 g, Y=93%) contained 0.6 w % diethyl ether as estimated by NMR. (Mp.>265° C.)

Example 3

Preparation of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride hexahydrate crystals for X-ray analysis

[0086] 6-Methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride (200 mg; see Example 2) was dissolved in a hot mixture of ethanol (15 mL) and water (5 mL). The resulting clear solution was left to stand at ambient temperature for 6 days. The resulting crystals were collected by decantation of the supernatant solution and dried in a vacuum oven at 45° C. for 15 hours.

Example 4

X-Ray Data Collection and Structure Refinement

[0087] A single crystal of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride (beige prism) prepared as described in Example 3 was mounted on a glass fiber with silicone grease. X-ray data was collected on a Nonius KappaCCD diffractometer (radiation source: Mo Kα radiation at λ=0.71073 Å; 900 frames, 1.0 deg/frame, 40 sec/deg). Certain data collection and structural refinement parameters are provided in Table 1. The structure was solved by direct methods. During the full-matrix least-squares refinement, XYZs for the piperazin-1-ium hydrogen H(16) and for the water hydrogens H(1wa), H(2wa), H(2wb), H(2wa), and H(3wb) were free to vary. The water hydrogens on O(4w), O(5w), and O(6w) were not observed and were not included in the refinement. XYZs for all other hydrogens rode on their respective carbons. See FIG. **1** for probability ellipsoids and atom labels.

TABLE 1

Formula	$C_{28}H_{43}ClFN_5O_7$
Formula weight	616.12
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c (No. 14)
Unit cell dimensions (Å, °)	a = 14.3790(3) b = 7.6300(2) c = 28.6350(7) alpha = 90 beta = 107.105(2) gamma = 90
Volume	3002.63(12) $Å^3$
Z, Calculated density	4, 1.363 Mg/m^3
Absorption coefficient	0.187 mm^{-1}
F(000)	1312
Crystal size	0.22 x 0.18 x 0.18 mm
Theta range for data collection	1.48 to 27.50 deg.
Limiting indices	18 <= h <= 18, −9 <= k <= 9, −37 <= l <= 37
Reflections collected/unique	50350/6885 [R(int) = 0.0877]
Completeness to theta = 27.50	100.0%
Absorption correction	Gaussian
Max. and min. transmission	0.97640 and 0.94840
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6884/8/420
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0511, wR2 = 0.1176
R indices (all data)	R1 = 0.0758, wR2 = 0.1339
Largest diff. peak and hole	0.463 and −0.369 e. $Å^{-3}$

Example 5

Atomic Coordinates

[0088] Atomic coordinates for non-hydrogen atoms of the structure provided herein are set out in Table 2. See FIG. **1** for atom labels.

TABLE 2

Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]•6H_2O$. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	3883(1)	−216(2)	3628(1)	31(1)
C(2)	3001(2)	−877(3)	3448(1)	35(1)
C(3)	2269(2)	−774(3)	3679(1)	36(1)
C(4)	2467(1)	91(3)	4113(1)	34(1)
C(5)	3387(1)	864(2)	4320(1)	28(1)
C(6)	3608(1)	1779(3)	4770(1)	31(1)
C(7)	4521(1)	2433(3)	4963(1)	30(1)
C(8)	5232(1)	2251(3)	4714(1)	30(1)
C(9)	5042(1)	1398(2)	4275(1)	27(1)
C(10)	4091(1)	662(2)	4064(1)	28(1)
O(11)	4849(1)	3304(2)	5396(1)	37(1)
C(12)	4202(2)	3422(3)	5691(1)	40(1)
N(13)	5787(1)	1120(2)	4046(1)	28(1)
C(14)	5632(1)	1974(3)	3568(1)	29(1)

TABLE 2-continued

Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(15)	6364(1)	1330(3)	3318(1)	30(1)
N(16)	7383(1)	1710(2)	3632(1)	26(1)
C(17)	7520(1)	860(3)	4120(1)	30(1)
C(18)	6768(1)	1521(3)	4352(1)	30(1)
C(19)	8163(1)	1189(3)	3398(1)	27(1)
C(20)	8049(1)	2254(3)	2932(1)	30(1)
C(21)	8912(1)	2038(3)	2731(1)	30(1)
N(22)	9818(1)	2495(2)	3104(1)	27(1)
C(23)	9962(1)	1285(3)	3520(1)	32(1)
C(24)	9163(1)	1499(3)	3763(1)	32(1)
C(25)	10659(1)	2621(2)	2942(1)	28(1)
C(26)	11496(1)	3490(2)	3257(1)	28(1)
N(27)	11430(1)	4236(2)	3681(1)	32(1)
C(28)	12222(2)	4962(3)	3975(1)	37(1)
C(29)	13120(2)	5061(3)	3876(1)	38(1)
C(30)	13191(2)	4398(3)	3448(1)	35(1)
C(31)	12372(1)	3586(3)	3124(1)	30(1)
C(32)	12367(1)	2863(3)	2671(1)	34(1)
C(33)	11577(2)	2100(3)	2362(1)	35(1)
C(34)	10719(2)	1970(3)	2504(1)	31(1)
F(35)	13207(1)	2995(2)	2544(1)	49(1)
Cl(36)	7675(1)	5852(1)	3752(1)	40(1)
O(1W)	4457(1)	−1359(3)	2802(1)	49(1)
O(2W)	5529(1)	5690(2)	2974(1)	50(1)
O(3W)	9951(1)	6541(3)	3825(1)	52(1)
O(4W)	10746(3)	7653(4)	4771(1)	113(1)
O(5W)	8412(3)	5623(5)	4900(1)	129(1)
O(6W)	9237(4)	8726(6)	5079(1)	127(2)

Example 6

Bond Lengths and Bond Angles

[0089] Bond lengths and angles for the structure provided herein are set out in Tables 3 and 4. See FIG. **1** for atom labels.

TABLE 3

Selected bond lengths [Å] and angles [deg] for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.

N(1)—C(2)	1.320(3)
N(1)—C(10)	1.369(2)
C(2)—C(3)	1.401(3)
C(3)—C(4)	1.362(3)
C(4)—C(5)	1.410(3)
C(5)—C(6)	1.417(3)
C(5)—C(10)	1.423(3)
C(6)—C(7)	1.360(3)
C(7)—O(11)	1.363(2)
C(7)—C(8)	1.415(3)
C(8)—C(9)	1.370(3)
C(9)—N(13)	1.426(2)
C(9)—C(10)	1.438(3)
O(11)—C(12)	1.431(2)
N(13)—C(18)	1.458(2)
N(13)—C(14)	1.473(2)
C(14)—C(15)	1.518(3)
C(15)—N(16)	1.505(2)
N(16)—C(17)	1.499(2)
N(16)—C(19)	1.519(2)
C(17)—C(18)	1.513(3)
C(19)—C(24)	1.527(3)
C(19)—C(20)	1.530(3)

TABLE 3-continued

Selected bond lengths [Å] and angles [deg] for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.

C(20)—C(21)	1.523(3)
C(21)—N(22)	1.463(2)
N(22)—C(25)	1.419(2)
N(22)—C(23)	1.474(2)
C(23)—C(24)	1.516(3)
C(25)—C(34)	1.377(3)
C(25)—C(26)	1.437(3)
C(26)—N(27)	1.369(2)
C(26)—C(31)	1.420(3)
N(27)—C(28)	1.322(3)
C(28)—C(29)	1.403(3)
C(29)—C(30)	1.357(3)
C(30)—C(31)	1.411(3)
C(31)—C(32)	1.409(3)
C(32)—C(33)	1.349(3)
C(32)—F(35)	1.363(2)
C(33)—C(34)	1.411(3)
C(2)—N(1)—C(10)	118.1(2)
N(1)—C(2)—C(3)	124.3(2)
C(4)—C(3)—C(2)	118.3(2)
C(3)—C(4)—C(5)	120.3(2)
C(4)—C(5)—C(6)	121.3(2)
C(4)—C(5)—C(10)	117.4(2)
C(6)—C(5)—C(10)	121.3(2)
C(7)—C(6)—C(5)	118.8(2)
C(6)—C(7)—O(11)	125.7(2)
C(6)—C(7)—C(8)	120.8(2)
O(11)—C(7)—C(8)	113.5(2)
C(9)—C(8)—C(7)	122.1(2)
C(8)—C(9)—N(13)	121.3(2)
C(8)—C(9)—C(10)	118.6(2)
N(13)—C(9)—C(10)	119.9(2)
N(1)—C(10)—C(5)	121.7(2)
N(1)—C(10)—C(9)	120.0(2)
C(5)—C(10)—C(9)	116.3(2)
C(7)—O(11)—C(12)	117.1(2)
C(9)—N(13)—C(18)	114.7(2)
C(9)—N(13)—C(14)	115.6(2)
C(18)—N(13)—C(14)	108.71(14)
N(13)—C(14)—C(15)	111.0(2)
N(16)—C(15)—C(14)	110.1(2)
C(17)—N(16)—C(15)	108.15(14)
C(17)—N(16)—C(19)	112.71(14)
C(15)—N(16)—C(19)	113.66(14)
N(16)—C(17)—C(18)	110.5(2)
N(13)—C(18)—C(17)	110.9(2)
N(16)—C(19)—C(24)	109.1(2)
N(16)—C(19)—C(20)	110.0(2)
C(24)—C(19)—C(20)	110.6(2)
C(21)—C(20)—C(19)	112.5(2)
N(22)—C(21)—C(20)	110.3(2)
C(25)—N(22)—C(21)	116.0(2)
C(25)—N(22)—C(23)	112.02(14)
C(21)—N(22)—C(23)	109.0(2)
N(22)—C(23)—C(24)	110.9(2)
C(23)—C(24)—C(19)	111.0(2)
C(34)—C(25)—N(22)	124.1(2)
C(34)—C(25)—C(26)	118.2(2)
N(22)—C(25)—C(26)	117.7(2)
N(27)—C(26)—C(31)	120.9(2)
N(27)—C(26)—C(25)	118.9(2)
C(31)—C(26)—C(25)	120.1(2)
C(28)—N(27)—C(26)	117.9(2)
N(27)—C(28)—C(29)	124.4(2)
C(30)—C(29)—C(28)	118.7(2)
C(29)—C(30)—C(31)	119.2(2)
C(32)—C(31)—C(30)	123.7(2)
C(32)—C(31)—C(26)	117.5(2)
C(30)—C(31)—C(26)	118.7(2)
C(33)—C(32)—F(35)	119.9(2)
C(33)—C(32)—C(31)	123.3(2)

TABLE 3-continued

Selected bond lengths [Å] and angles [deg] for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.	
F(35)—C(32)—C(31)	116.8(2)
C(32)—C(33)—C(34)	118.7(2)
C(25)—C(34)—C(33)	122.2(2)

[0090]

TABLE 4

Bond lengths [Å] and angles [deg] for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.	
N(1)—C(2)	1.320(3)
N(1)—C(10)	1.369(2)
C(2)—C(3)	1.401(3)
C(2)—H(2)	0.95
C(3)—C(4)	1.362(3)
C(3)—H(3)	0.95
C(4)—C(5)	1.410(3)
C(4)—H(4)	0.95
C(5)—C(6)	1.417(3)
C(5)—C(10)	1.423(3)
C(6)—C(7)	1.360(3)
C(6)—H(6)	0.95
C(7)—O(11)	1.363(2)
C(7)—C(8)	1.415(3)
C(8)—C(9)	1.370(3)
C(8)—H(8)	0.95
C(9)—N(13)	1.426(2)
C(9)—C(10)	1.438(3)
O(11)—C(12)	1.431(2)
C(12)—H(12A)	0.98
C(12)—H(12B)	0.98
C(12)—H(12C)	0.98
N(13)—C(18)	1.458(2)
N(13)—C(14)	1.473(2)
C(14)—C(15)	1.518(3)
C(14)—H(14A)	0.99
C(14)—H(14B)	0.99
C(15)—N(16)	1.505(2)
C(15)—H(15A)	0.99
C(15)—H(15B)	0.99
N(16)—C(17)	1.499(2)
N(16)—C(19)	1.519(2)
N(16)—H(16)	0.94(2)
C(17)—C(18)	1.513(3)
C(17)—H(17A)	0.99
C(17)—H(17B)	0.99
C(18)—H(18A)	0.99
C(18)—H(18B)	0.99
C(19)—C(24)	1.527(3)
C(19)—C(20)	1.530(3)
C(19)—H(19)	1.00
C(20)—C(21)	1.523(3)
C(20)—H(20A)	0.99
C(20)—H(20B)	0.99
C(21)—N(22)	1.463(2)
C(21)—H(21A)	0.99
C(21)—H(21B)	0.99
N(22)—C(25)	1.419(2)
N(22)—C(23)	1.474(2)
C(23)—C(24)	1.516(3)
C(23)—H(23A)	0.99
C(23)—H(23B)	0.99
C(24)—H(24A)	0.99
C(24)—H(24B)	0.99
C(25)—C(34)	1.377(3)
C(25)—C(26)	1.437(3)
C(26)—N(27)	1.369(2)
C(26)—C(31)	1.420(3)
N(27)—C(28)	1.322(3)
C(28)—C(29)	1.403(3)

TABLE 4-continued

Bond lengths [Å] and angles [deg] for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.	
C(28)—H(28)	0.95
C(29)—C(30)	1.357(3)
C(29)—H(29)	0.95
C(30)—C(31)	1.411(3)
C(30)—H(30)	0.95
C(31)—C(32)	1.409(3)
C(32)—C(33)	1.349(3)
C(32)—F(35)	1.363(2)
C(33)—C(34)	1.411(3)
C(33)—H(33)	0.95
C(34)—H(34)	0.95
O(1W)—H(1WA)	0.82(3)
O(1W)—H(1WB)	0.93(3)
O(2W)—H(2WA)	0.89(3)
O(2W)—H(2WB)	0.95(3)
O(3W)—H(3WA)	0.85(3)
O(3W)—H(3WB)	0.87(3)
O(4W)—H(4WA)	0.89(6)
O(4W)—H(4WB)	0.93(5)
O(5W)—H(5WA)	0.91(2)
O(5W)—H(5WB)	0.91(2)
O(6W)—H(6WA)	0.90(4)
O(6W)—H(6WB)	0.90(3)
C(2)—N(1)—C(10)	118.1(2)
N(1)—C(2)—C(3)	124.3(2)
N(1)—C(2)—H(2)	117.9
C(3)—C(2)—H(2)	117.9
C(4)—C(3)—C(2)	118.3(2)
C(4)—C(3)—H(3)	120.9
C(2)—C(3)—H(3)	120.9
C(3)—C(4)—C(5)	120.3(2)
C(3)—C(4)—H(4)	119.8
C(5)—C(4)—H(4)	119.8
C(4)—C(5)—C(6)	121.3(2)
C(4)—C(5)—C(10)	117.4(2)
C(6)—C(5)—C(10)	121.3(2)
C(7)—C(6)—C(5)	118.8(2)
C(7)—C(6)—H(6)	120.6
C(5)—C(6)—H(6)	120.6
C(6)—C(7)—O(11)	125.7(2)
C(6)—C(7)—C(8)	120.8(2)
O(11)—C(7)—C(8)	113.5(2)
C(9)—C(8)—C(7)	122.1(2)
C(9)—C(8)—H(8)	119.0
C(7)—C(8)—H(8)	119.0
C(8)—C(9)—N(13)	121.3(2)
C(8)—C(9)—C(10)	118.6(2)
N(13)—C(9)—C(10)	119.9(2)
N(1)—C(10)—C(5)	121.7(2)
N(1)—C(10)—C(9)	120.0(2)
C(5)—C(10)—C(9)	118.3(2)
C(7)—O(11)—C(12)	117.1(2)
O(11)—C(12)—H(12A)	109.5
O(11)—C(12)—H(12B)	109.5
H(12A)—C(12)—H(12B)	109.5
O(11)—C(12)—H(12C)	109.5
H(12A)—C(12)—H(12C)	109.5
H(12B)—C(12)—H(12C)	109.5
C(9)—N(13)—C(18)	114.7(2)
C(9)—N(13)—C(14)	115.6(2)
C(18)—N(13)—C(14)	108.71(14)
N(13)—C(14)—C(15)	111.0(2)
N(13)—C(14)—H(14A)	109.4
C(15)—C(14)—H(14A)	109.4
N(13)—C(14)—H(14B)	109.4
C(15)—C(14)—H(14B)	109.4
H(14A)—C(14)—H(14B)	108.0
N(16)—C(15)—C(14)	110.1(2)
N(16)—C(15)—H(15A)	109.6
C(14)—C(15)—H(15A)	109.6
N(16)—C(15)—H(15B)	109.6
C(14)—C(15)—H(15B)	109.6
H(15A)—C(15)—H(15B)	108.1
C(17)—N(16)—C(15)	108.15(14)

TABLE 4-continued

Bond lengths [Å] and angles [deg] for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.

C(17)—N(16)—C(19)	112.71(14)
C(15)—N(16)—C(19)	113.66(14)
C(17)—N(16)—H(16)	107.6(13)
C(15)—N(16)—H(16)	107.8(13)
C(19)—N(16)—H(16)	106.7(13)
N(16)—C(17)—C(18)	110.5(2)
N(16)—C(17)—H(17A)	109.6
C(18)—C(17)—H(17A)	109.6
N(16)—C(17)—H(17B)	109.6
C(18)—C(17)—H(17B)	109.6
H(17A)—C(17)—H(17B)	108.1
N(13)—C(18)—C(17)	110.9(2)
N(13)—C(18)—H(18A)	109.5
C(17)—C(18)—H(18A)	109.5
N(13)—C(18)—H(18B)	109.5
C(17)—C(18)—H(18B)	109.5
H(18A)—C(18)—H(18B)	108.0
N(16)—C(19)—C(24)	109.1(2)
N(16)—C(19)—C(20)	110.0(2)
C(24)—C(19)—C(20)	110.6(2)
N(16)—C(19)—H(19)	109.0
C(24)—C(19)—H(19)	109.0
C(20)—C(19)—H(19)	109.0
C(21)—C(20)—C(19)	112.5(2)
C(21)—C(20)—H(20A)	109.1
C(19)—C(20)—H(20A)	109.1
C(21)—C(20)—H(20B)	109.1
C(19)—C(20)—H(20B)	109.1
H(20A)—C(20)—H(20B)	107.8
N(22)—C(21)—C(20)	110.3(2)
N(22)—C(21)—H(21A)	109.6
C(20)—C(21)—H(21A)	109.6
N(22)—C(21)—H(21B)	109.6
C(20)—C(21)—H(21B)	109.6
H(21A)—C(21)—H(21B)	108.1
C(25)—N(22)—C(21)	116.0(2)
C(25)—N(22)—C(23)	112.02(14)
C(21)—N(22)—C(23)	109.0(2)
N(22)—C(23)—C(24)	110.9(2)
N(22)—C(23)—H(23A)	109.4
C(24)—C(23)—H(23A)	109.4
N(22)—C(23)—H(23B)	109.4
C(24)—C(23)—H(23B)	109.4
H(23A)—C(23)—H(23B)	108.0
C(23)—C(24)—C(19)	111.0(2)
C(23)—C(24)—H(24A)	109.4
C(19)—C(24)—H(24A)	109.4
C(23)—C(24)—H(24B)	109.4
C(19)—C(24)—H(24B)	109.4
H(24A)—C(24)—H(24B)	108.0
C(34)—C(25)—N(22)	124.1(2)
C(34)—C(25)—C(26)	118.2(2)
N(22)—C(25)—C(26)	117.7(2)
N(27)—C(26)—C(31)	120.9(2)
N(27)—C(26)—C(25)	118.9(2)
C(31)—C(26)—C(25)	120.1(2)
C(28)—N(27)—C(26)	117.9(2)
N(27)—C(28)—C(29)	124.4(2)
N(27)—C(28)—H(28)	117.8
C(29)—C(28)—H(28)	117.8
C(30)—C(29)—C(28)	118.7(2)
C(30)—C(29)—H(29)	120.7
C(28)—C(29)—H(29)	120.7
C(29)—C(30)—C(31)	119.2(2)
C(29)—C(30)—H(30)	120.4
C(31)—C(30)—H(30)	120.4
C(32)—C(31)—C(30)	123.7(2)
C(32)—C(31)—C(26)	117.5(2)
C(30)—C(31)—C(26)	118.7(2)
C(33)—C(32)—F(35)	119.9(2)
C(33)—C(32)—C(31)	123.3(2)
F(35)—C(32)—C(31)	116.8(2)
C(32)—C(33)—C(34)	118.7(2)
C(32)—C(33)—H(33)	120.7

TABLE 4-continued

Bond lengths [Å] and angles [deg] for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.

C(34)—C(33)—H(33)	120.7
C(25)—C(34)—C(33)	122.2(2)
C(25)—C(34)—H(34)	118.9
C(33)—C(34)—H(34)	118.9
H(1WA)—O(1W)—H(1WB)	109(3)
H(2WA)—O(2W)—H(2WB)	108(3)
H(3WA)—O(3W)—H(3WB)	100(3)
H(4WA)—O(4W)—H(4WB)	101(5)
H(5WA)—O(5W)—H(5WB)	103(2)
H(6WA)—O(6W)—H(6WB)	109(3)

Example 7

Anisotropic Displacement Parameters

[0091] Anisotropic displacement parameters for non-hydrogen atoms of the structure provided herein are set out in Table 5. See FIG. **1** for atom labels.

TABLE 5

Anisotropic displacement parameters ($Å^2 \times 10^3$) for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$. The anisotropic displacement factor exponent takes the form: $-2pi^2 [h^2 a^{*2} U_{11} + \ldots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
N(1)	30(1)	28(1)	34(1)	0(1)	9(1)	0(1)
C(2)	33(1)	32(1)	39(1)	−3(1)	9(1)	−1(1)
C(3)	27(1)	35(1)	45(1)	2(1)	6(1)	−1(1)
C(4)	27(1)	36(1)	40(1)	5(1)	13(1)	1(1)
C(5)	26(1)	28(1)	31(1)	6(1)	8(1)	3(1)
C(6)	30(1)	33(1)	34(1)	5(1)	15(1)	4(1)
C(7)	35(1)	28(1)	28(1)	1(1)	13(1)	2(1)
C(8)	26(1)	30(1)	36(1)	1(1)	12(1)	−2(1)
C(9)	27(1)	25(1)	31(1)	4(1)	12(1)	3(1)
C(10)	27(1)	25(1)	32(1)	3(1)	10(1)	2(1)
O(11)	37(1)	43(1)	36(1)	−10(1)	18(1)	−6(1)
C(12)	48(1)	40(1)	40(1)	−6(1)	25(1)	−3(1)
N(13)	26(1)	31(1)	28(1)	2(1)	10(1)	1(1)
C(14)	27(1)	31(1)	29(1)	2(1)	9(1)	0(1)
C(15)	24(1)	36(1)	28(1)	−1(1)	9(1)	−1(1)
N(16)	24(1)	29(1)	27(1)	1(1)	9(1)	0(1)
C(17)	27(1)	37(1)	28(1)	6(1)	9(1)	1(1)
C(18)	26(1)	35(1)	28(1)	3(1)	10(1)	0(1)
C(19)	26(1)	30(1)	29(1)	−1(1)	12(1)	2(1)
C(20)	25(1)	38(1)	26(1)	1(1)	8(1)	1(1)
C(21)	28(1)	36(1)	29(1)	−2(1)	10(1)	−2(1)
N(22)	23(1)	33(1)	27(1)	1(1)	10(1)	−2(1)
C(23)	27(1)	38(1)	32(1)	6(1)	11(1)	3(1)
C(24)	27(1)	40(1)	29(1)	6(1)	10(1)	2(1)
C(25)	27(1)	26(1)	31(1)	2(1)	11(1)	1(1)
C(26)	28(1)	26(1)	31(1)	3(1)	10(1)	2(1)
N(27)	32(1)	32(1)	32(1)	−1(1)	12(1)	−2(1)
C(28)	39(1)	35(1)	36(1)	−3(1)	9(1)	−2(1)
C(29)	32(1)	33(1)	44(1)	1(1)	5(1)	−4(1)
C(30)	27(1)	32(1)	45(1)	6(1)	9(1)	2(1)
C(31)	29(1)	27(1)	36(1)	7(1)	12(1)	4(1)
C(32)	29(1)	36(1)	42(1)	6(1)	20(1)	6(1)
C(33)	40(1)	35(1)	36(1)	−1(1)	20(1)	2(1)
C(34)	32(1)	31(1)	33(1)	−1(1)	12(1)	−1(1)
F(35)	36(1)	63(1)	56(1)	−3(1)	28(1)	−1(1)
Cl(36)	44(1)	38(1)	41(1)	−3(1)	17(1)	1(1)
O(1W)	55(1)	52(1)	41(1)	−4(1)	17(1)	8(1)
O(2W)	56(1)	49(1)	47(1)	5(1)	16(1)	4(1)
O(3W)	44(1)	51(1)	60(1)	−8(1)	15(1)	4(1)
O(4W)	154(3)	97(2)	65(2)	−22(2)	−3(2)	7(2)
O(5W)	144(3)	187(3)	47(1)	8(2)	14(2)	72(3)
O(6W)	164(4)	103(3)	79(3)	−35(2)	−20(3)	57(3)

Example 8

Hydrogen Coordinates

[0092] Hydrogen coordinates are provided in Table 6.

TABLE 6

Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for $[C_{28}H_{31}FN_5O^{1+}][Cl^{1-}]\cdot 6H_2O$.

	x	y	z	U(eq)
H(2)	2854	−1460	3142	42
H(3)	1650	−1293	3536	44
H(4)	1983	174	4278	40
H(6)	3128	1932	4934	37
H(8)	5860	2735	4856	36
H(12A)	4521	4061	5992	60
H(12B)	4032	2240	5772	60
H(12C)	3609	4044	5510	60
H(14A)	5696	3260	3614	35
H(14B)	4964	1721	3358	35
H(15A)	6283	52	3260	35
H(15B)	6246	1920	2998	35
H(16)	7439(16)	2933(33)	3683(8)	39
H(17A)	8180	1124	4336	36
H(17B)	7460	−427	4079	36
H(18A)	6878	968	4676	35
H(18B)	6839	2805	4400	35
H(19)	8091	−85	3313	33
H(20A)	7448	1878	2680	36
H(20B)	7976	3508	3002	36
H(21A)	8945	810	2625	36
H(21B)	8825	2806	2442	36
H(23A)	10601	1520	3762	38
H(23B)	9965	63	3405	38
H(24A)	9190	2697	3899	38
H(24B)	9268	656	4036	38
H(28)	12180	5449	4274	44
H(29)	13668	5581	4105	45
H(30)	13785	4480	3368	42
H(33)	11598	1659	2055	42
H(34)	10165	1416	2290	38
H(1WA)	4414(22)	−1011(42)	3066(12)	73
H(1WB)	4837(22)	−2365(44)	2853(11)	73
H(2WA)	5538(22)	5121(43)	2705(12)	76
H(2WB)	6186(24)	5836(41)	3171(11)	76
H(3WA)	10241(24)	5607(45)	3787(11)	78
H(3WB)	9379(25)	6127(43)	3808(11)	78
H(4WA)	11119(42)	6708(79)	4867(21)	169
H(4WB)	10444(38)	7374(74)	4445(20)	169
H(5WA)	8159(34)	5712(80)	4571(5)	194
H(5WB)	9064(9)	5622(93)	4945(19)	194
H(6WA)	9655(28)	8050(70)	4978(2)	190
H(6WB)	9437(37)	9848(27)	5092(7)	190

Example 9

Preparation of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline tris(hydrochloride) dihydrate

Step 1: 5-Fluoro-8 chloroquinoline

[0093] To a mixture of (5.0 g) 2-chloro-5-fluoroaniline (commercially available, 6.0 g), glycerol (6.0 g) and m-nitrobenzene sulfonic acid sodium salt (11.0 g), was added 20 mL of 70% sulfuric acid dropwise. The reaction temperature was raised to 140° C. for 2 h. The mixture was then cooled, poured on ice water and filtered through Celite. The filtrate was neutralized with NaOH and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The crude product was purified by flash chromatography on silica gel using 100% CH_2Cl_2 to give 3.7 g of the desired product of a yellow solid; MP=74-76° C.; MS (ES) m/z (relative intensity): 182 $(M+H)^+$ (100).

Step 2: 8-(1,4-Dioxa-8-azaspiro[4,5]dec-5-yl)-5-fluoroquinoline

[0094] To a solution of 5-fluoro-8-chloroquinoline (Step 1, 1.12 g) in 20 mL of anhydrous tetrahydrofuran, was added 0.085 g of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 0.085 g), sodium tert-butoxide (0.83 g), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)-biphenyl (CYMAP, 0.036 g), and 1,4-dioxo-8-azaspiro-4,5-decane (1.05 g). The mixture was refluxed for 6 hours under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature, diluted with ether, filtered through celite and concentrated on a rotary evaporator. The crude material was then purified by flash chromatography on silica gel using hexane/ethyl acetate to give 0.700 g of the desired product as a brown oil; MS (ES) m/z (relative intensity): 289 $(M+H)^+$ (100).

Step 3: 1-(5-Fluoroquinolin-8-yl)piperidin-4-one

[0095] A solution of 8-(1,4-dioxa-8-azaspiro[4,5]dec-5-yl)-5-fluoroquinoline (Step 2, 2.1 g)) in 10 mL of 1:1 tetrahydrofuran/2N aqueous HCl was stirred at room temperature overnight. The reaction mixture was diluted with water, made basic with 1N aqueous NaOH and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator to give 1.68 g of the desired product as a yellow solid which was pure enough to use in subsequent reactions; MS m/z=245 $[M+H]^+$.

Step 4: 8-Chloro-6-hydroxyquinoline

[0096] In a 500 mL 3-necked flask equipped with a mechanical stirrer, a reflux condenser, were added in order ferrous sulfate (2.0 g), 4-amino-3-chlorophenol hydrochloride (6.4 g, commercially available), nitrobenzene (2.9 mL) and a solution of boric acid (3.0 g) in glycerol (16 g). Then concentrated sulfuric acid (9 mL) was added drop by drop with cooling. The ice bath was removed and replaced by an oil bath and the mixture was heated cautiously to 120° C. for 2 hours, then at 150° C. and kept stirring under this temperature for 20 hours. After cooling, the reaction was poured on crushed ice and the resulting solution was neutralized with K_2CO_3. The product separated as a light brown solid that was filtered off, washed with water and hexanes and dried in a vacuum oven (35° C.) overnight giving 7 g (77%) of the desired product. MS (ES) m/z (relative intensity): 180 (M++−H, 100).

Step 5: 8-Chloro-6-methoxyquinoline

[0097] To a solution of 3.3 g of 8-chloro-6-hydroxyquinoline (Step 4, 3.3 g) in dimethylformamide was added K_2CO_3 (3.8 g), followed by iodomethane (5.2 g). The mixture was stirred at room temperature overnight. Water was then added and the aqueous mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator. The crude product was purified by flash chromatography on silica gel using 100% CH_2Cl_2, to give 2.2 g of the desired product as a beige solid; MP=74-75° C.; MS (ES) m/z (relative intensity): 194 $(M+H)^+$ (100).

Step 6: 6-Methoxy-8-[1-(tert-butoxycarbonyl)-4-piperazino]quinoline

[0098] To a mixture of 8-chloro-6-methoxyquinoline (Step 5, 2.7 g) in anhydrous tetrahydrofuran, was added tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 0.064 g), sodium tert-butoxide (1.9 g), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (CYMAP, 0.08 g) and tert-butoxycarbonylpiperazine (3.4 g). The mixture was refluxed for 5 hours under a nitrogen atmosphere. The reaction was then cooled to room temperature, diluted with ether, filtered through Celite and concentrated on a rotary evaporator. The crude material was purified by flash chromatography using 100% CH_2Cl_2 to give 4.0 g of the desired product as a beige solid; mp=92-93° C.; MS (ES) m/z (relative intensity): 344 (M^++H) (100).

Step 7: 6-Methoxy-8-piperazinoquinoline

[0099] To a solution of 6-methoxy-8-[1-(tert-butoxycarbonyl)-4-piperazino]quinoline (Step 6, 4.0 g) in 20 mL ofdDioxane was added 10 mL of 4 N HCl/dioxane. The mixture was stirred at room temperature overnight. The resulting precipitate was collected by vacuum filtration, dissolved in water, neutralized with aqueous sodium hydroxide and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on a rotary evaporator to give 2.8 g of the desired product as a beige solid; MP=105-107° C.; MS (ES) m/z (relative intensity): 244 $(M+H)^+$ (100).

Step 8: 5-Fluoro-8-(4-(4-(6-methoxyquinolin-8-yl)piperazin-1-yl)piperidin-1-yl)quinoline

[0100] 1-(5-Fluoro-quinolin-8-yl)-piperidin-4-one (Step 3, 0.25 g, 0.001 mol) and 6-methoxy-8-piperazinoquinoline (Step 7, 0.25 g, 0.001 mol) were stirred in 20 mL of anhydrous methanol. 1.1 eq, (0.07 gm) of sodium cyanoborohydride was added and the reaction was stirred at room temperature for eighteen hours. The reaction mixture was concentrated on a rotary evaporator and the residue was taken up in ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator. The desired product was obtained by flash chromatography on silica gel column using ethyl acetate.

Step 9. 6-Methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline trihydrochloride dihydrate

[0101] The free base product of Step 8 was converted to the trihydrochloride salt using methanolic HCl to yield 0.15 gm (24%) of the title compound as a yellow solid. Mp: 200-202° C.; MS (ES) m/z (relative intensity): 472 (M+H)+ (100).

[0102] Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patents, patent applications, and journal literature, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A hydrochloric acid salt of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline.

2. The salt of claim 1 which is a monohydrochloric acid salt or trishydrochloric acid salt.

3. The salt of claim 1 which is crystalline.

4. The salt of claim 1 which is hydrated.

5. The salt of claim 4 which is a hexahydrate or a dihydrate.

6. A crystalline form of a monohydrochloric acid salt of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline having a monoclinic space group.

7. The crystalline form of claim 6 having a space group P2(1)/c (No. 14).

8. The crystalline form of claim 7 having unit cell parameters:

a=14.4 Å;

b=7.6 Å;

c=28.6 Å; and

beta=107.1°.

9. A process for preparing the crystalline form of claim 6 comprising precipitating said crystalline form from an aqueous solution of 6-methoxy-8-[4-(1-(5-fluoro)-quinolin-8-yl-piperidin-4-yl)-piperazin-1-yl]-quinoline monohydrochloride.

10. The process of claim 9 wherein said aqueous solution comprises an alcohol.

11. The process of claim 10 wherein said alcohol is ethanol.

12. The process of claim 9 wherein the volume ratio of water to alcohol is about 1:1 to about 1:10.

13. The process of claim 9 wherein the volume ratio of water to alcohol is about 1:3.

14. A crystalline form prepared by the process of claim 9.

15. A method for treating a 5-HT_{1A}-related disorder in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a salt or crystalline form of claim 1.

16. The method of claim 15 wherein the 5-HT_{1A}-related disorder is a cognition-related disorder or an anxiety-related disorder.

17. The method of claim 16 wherein the cognition-related disorder is dementia, Parkinson's disease, Huntington's disease, Alzheimer's disease, cognitive deficits associated with Alzheimer's disease, mild cognitive impairment, or schizophrenia.

18. The method of claim 16, wherein the anxiety-related disorder is attention deficit disorder, obsessive compulsive disorder, substance addiction, withdrawal from substance addiction, premenstrual dysphoric disorder, social anxiety disorder, anorexia nervosa, or bulimia nervosa.

19. A method for treating Alzheimer's disease in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a salt or crystalline form of claim 1.

20. A method for treating mild cognitive impairment (MCI) in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a compound or crystalline form of claim 1.

21. A method for treating depression in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of a salt or crystalline form of claim 1.

22. The method of any one of claims 15 to 21 further comprising administering a second therapeutic agent.

23. The method of claim 22 wherein the second therapeutic agent is an anti-depressant agent, an anti-anxiety agent, anti-psychotic agent, or a cognitive enhancer.

24. The method of claim 22 wherein the second therapeutic agent is a selective serotonin reuptake inhibitor.

25. The method of claim 24 wherein the second therapeutic agent is fluoxetine, fluvoxamine, paroxetine, sertaline, clonazepam, diazepam, buspirone, haloperidol, olanzapine, or clozapine.

26. The method of claim 22 wherein the second therapeutic agent is a cholinesterase inhibitor.

27. The method of claim 26 wherein the second therapeutic agent is tacrine, donepezil, rivastigmine, or galantamine.

28. A method for treating sexual dysfunction associated with drug treatment in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a salt or crystalline form of claim 1.

29. The method of claim 28 wherein the drug treatment is antidepressant drug treatment, antipsychotic drug treatment, or anticonvulsant drug treatment.

30. A method of improving sexual function in a patient in need thereof, the method comprising administering to the patient an effective amount of a salt or crystalline form of claim 1.

31. A composition comprising a salt or crystalline form of claim 1 and at least one pharmaceutically acceptable carrier.

32. The composition of claim 31 further comprising a second therapeutic agent.

33. The composition of claim 32 wherein said second therapeutic agent is an anti-depressant agent, an anti-anxiety agent, anti-psychotic agent, or a cognitive enhancer.

34. The composition of claim 32 wherein said second therapeutic agent is a selective serotonin reuptake inhibitor.

35. The composition of claim 34 wherein said second therapeutic agent is fluoxetine, fluvoxamine, paroxetine, sertaline, clonazepam, diazepam, buspirone, haloperidol, olanzapine, or clozapine.

36. The composition of claim 32 wherein said second therapeutic agent is a cholinesterase inhibitor.

37. The composition of claim 36 wherein said second therapeutic agent is tacrine, donepezil, rivastigmine, or galantamine.

* * * * *