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(71) Applicant *(for all designated States except US)*: **NUPATHE INC.** [US/US]; 227 Washington St., Suite 200, Conshohocken, PA 19428 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SIEGEL, Steven J.** [US/US]; 86 Highpoint Dr., Berwyn, PA 19312 (US). **SEBREE, Terri B.** [US/US]; 922 Merion Square Road, Gladwyne, PA 19035 (US).

(74) Agents: **HANLEY, Elizabeth A.** et al.; Lahive & Cockfield, LLP, One Post Office Square, Boston, MA 02109-2127 (US).

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(54) Title: IMPLANTS FOR THE TREATMENT OF PSYCHIATRIC STATES

(57) Abstract: Biodegradable implants comprising N-phenyl substituted indolyl compounds are described.

IMPLANTS FOR THE TREATMENT OF PSYCHIATRIC STATES

Related Applications:

This application claims priority to U.S. Provisional Patent Application Serial No. 60/903,934, filed on February 28, 2007, the entire contents of which are hereby incorporated herein by reference.

Background of the Invention:

Schizophrenia is a serious brain disorder that affects approximately 1% of the human population. The cause of this complex and devastating disease remains elusive, although genetic, nutritional, environmental, and developmental factors have been considered. A combination of clinical, neuroimaging, and postmortem studies have implicated the dorsal prefrontal cortex (PFC) as a prominent site of dysfunction in schizophrenia.

Schizophrenia is typically characterized as a disorder of thinking and cognition, as contrasted to other disorders of mental faculties, such as mood, social behavior, and those affecting learning, memory, and intelligence. Schizophrenia is generally characterized by psychotic episodes during which an individual may lose the ability to test reality or may have hallucinations, delusions, incoherent thinking, and even disordered memory. There are varying forms of schizophrenia differing in severity, from a schizotypal disorder to a catatonic state.

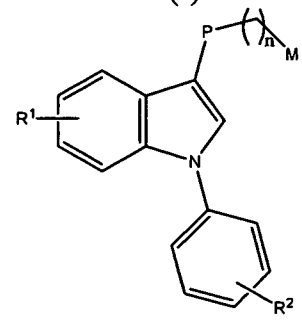
There is strong evidence for a genetic linkage of schizophrenia. Historically, there have been a number of studies on monozygotic twins of schizophrenics that indicated that 30 50% of the twins also had schizophrenia. The fact that this number is not 100% indicates that there are other factors involved in this disease process that may protect some of these individuals from the disease. It is apparent from a number of studies that the patterns of inheritance in most forms of schizophrenia are more complex than the classical dominant or recessive Mendelian inheritance.

Until the 1950's there were no specific, effective treatments for schizophrenia. Antipsychotic drugs were identified in the 1950's, and these drugs were found to produce a dramatic improvement in the psychotic phase of the illness. Reserpine was the first of these drugs to be used and was followed by typical antipsychotic drugs including phenothiazines, the butyrophenones, and the thioxanthenes. A new group of therapeutic drugs, typified by clozapine, has been developed and were referred to as "a typical" antipsychotics. Haloperidol has been employed extensively in the treatment of schizophrenia and is one of the currently preferred options for treatment. When these

drugs are taken over the course of at least several weeks, they mitigate or eliminate delusions, hallucinations, and some types of disordered thinking.

Summary of the Invention:

The invention pertains, at least in part, to a method for treating a subject for a disorder by administering to a subject a biodegradable implant comprising an N-phenyl substituted indolyl compound of formula (I):



(I)

wherein:

R^1 and R^2 are each independently halogen, hydroxyl, amino, thio, nitro, alkyl, alkenyl, alkynyl, aryl, or cyano;

P is a saturated cyclic moiety;

n is 0, 1, or 2;

M is a heterocycle; or a pharmacuetically acceptable salt thereof.

In a further embodiment, the compound of formula (I) is sertindole (5-chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon -1-yl)ethyl)-4-piperidy)1H-indole).

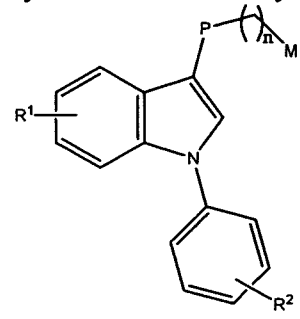
In another embodiment, the invention includes a biodegradable implant, which includes a compound of formula (I), such as sertindole, and a biodegradable polymer. In a further embodiment, the disorder is a psychiatric disorder such as, but not limited to, schizophrenia.

In yet another embodiment, the invention also pertains, at least in part, to a method for maintaining a therapeutic plasma level of a compound of formula (I), e.g., sertindole, in a subject. The method includes administering to the subject an implant comprising a biodegradable polymer and a compound of formula (I), such that the plasma level of the compound is maintained for at least one day.

In a further embodiment, the invention also pertains at least in part, to a method for treating a subject for schizophrenia. The method includes administering to a subject a biodegradable implant, wherein the implant comprises an effective amount of a compound of formula (I), e.g., sertindole, to treat schizophrenia.

Detailed Description of the Invention:

In one embodiment, the invention pertains to a method for treating a subject for a disorder treatable by administration of compounds of the invention. The method includes administering to the subject a biodegradable implant, which comprises an effective amount of an N-phenyl substituted indolyl compound of formula (I):



(I)

wherein:

R^1 and R^2 are each independently hydrogen, halogen, hydroxyl, amino, thio, nitro, alkyl, alkenyl, aryl, cyano or alkynyl;

P is a saturated substituted or unsubstited cyclic moiety;

n is 0, 1, 2, or 3;

M is a substituted or unsubstituted heterocycle; or a pharmacuetically acceptable salt thereof.

In a further embodiment, R^1 and R^2 are each indpendently halogen. In a further embodiment, R^1 is chlorine and R^2 is fluorine.

In another further embodiment, P is a saturated heterocyclic moeity, e.g., piperidine. In a further embodiment, the $-(CH_2)_n-$ linker is attached to P through N. In a further embodiment, n is 2. In a further embodiment, M comprises one or more nitrogen atoms and/or carbonyl moieties. In a further embodiment, M is imidazolidin-2-one. In a further embodiment, the compound of formula (I) is sertindole (5-chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon -1-yl)ethyl)-4-piperidy)1H-indole), or a pharmaceutically acceptable salt thereof.

Examples of disorders which are treatable by administration of the compounds of the invention include those related to the modulation, inhibition, or antagonism of the serotonin and/or serotonin receptors. Examples of disorders which may be related to serotonin receptor activity include anxiety, depression, hypertension, cognitive disorders, psychosis, sleep disorders, gastric motility disorders, sexual dysfunction, brain trauma, memory loss, appetite disorders and obesity, substance abuse, obsessive-compulsive disease, panic disorder and migraine.

In a further embodiment, the disorder treatable by administration of the compounds of the invention is a psychiatric state. The term "psychiatric state" includes states which can be treated by the administration of an N-phenyl substituted indolyl compound of formula (I), such as, but not limited to, sertindole. The term "psychiatric

states" include "psychiatric disorders" which are pathological conditions of the brain characterized by identifiable symptoms that results in abnormalities in cognition, emotion or mood, or the highest integrative aspects of behavior. These states may vary in severity of symptoms, duration, and functional impairment. Psychiatric states afflict millions of people worldwide resulting in tremendous human suffering and economic burden due to lost productivity.

Psychiatric states can be classified into various categories based on etiology and symptomatology. Such a classification system includes somatoform disorders, anxiety disorders, dissociative disorders, mood disorders, personality disorders, psychosexual disorders, schizophrenia and related disorders, drug abuse and dependence, and eating disorders.

In some cases the psychiatric states may be acute, lasting only for several weeks to months. In other instances the disorder is chronic, lasting for years or even decades. Psychiatric disorders afflict people of all ages. The initial age for onset of a psychiatric disorder also varies. For example, children may suffer attention deficit hyperactive disorder, depression and disruptive disorders. Adolescence may suffer from depression, eating disorders, and may experience the onset of schizophrenia. Other individuals may only experience psychiatric disorders in adulthood.

In a further embodiment, the pyschiatric state is schizophrenia. The term "schizophrenia" includes a group of mental disorders characterized by disruptions in thinking and perception. In a clinical evaluation, schizophrenia is commonly marked by "positive symptoms" such as auditory hallucinations (especially hearing voices), disorganized thought processes and delusions as well as "negative symptoms" which include affective flattening, alogia, avolition, and anhedonia.

The term "implant" includes surgically implantable devices comprised of one or more sections. The sections may be of any size which allows the implant to perform its intended function. In one embodiment, the sections and/or implant are removable from the subject. In another embodiment, the implant is comprised of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more discrete sections. In another embodiment, the section may be rod shaped. In a further embodiment, the implant is comprised of a biocompatible and/or biodegradable polymer. Preferably, the implants are removable through out the time period when the compound of formula (I) is being released to the subject at therapeutic levels. The sections may be shaped as rods, disks, crescents, cones, spheres or any other shape which allows for the implant to perform its intended function. In one embodiment, the sections are macroscopic (e.g., at least 1 mm in diameter). In a further embodiment, the sections are rod shaped. In another further embodiment, the diameter of the sections are about 0.5 to about 5 mm in diameter and about 0.5 cm to about 10 cm in length. In another further embodiment, the diameter of the sections are about 0.5 to

about 5 mm in diameter and about 0.5 cm to about 5 cm in length. In another further embodiment, the sections are about 1 mm to about 3 mm in diameter and about 1 cm to about 3 cm in length.

In certain embodiments, the term "implant" also includes microparticles. The microparticles are particles of a spherical shape, although sometimes the microparticles may be irregularly shaped. The microparticles can vary in size, ranging from submicron to 1 mm or less. In a further embodiment, the microparticles are 1-500 microns, more preferably, 25-180 microns, and are prepared such that administration of the microparticles to a subject can be carried out with a standard gauge needle.

The microparticles may be administered to a subject in a single administration, releasing the drug in a constant or pulsed manner into the subject and eliminating the need for repetitive injections. The microparticles can be mixed by size or by type so as to provide for the delivery of the compound of formula (I) to the subject in a multiphasic manner and/or in a manner that provides different agents to the subject at different times, or a mixture of agents at the same time.

The microparticles can be prepared by any method capable of producing microparticles. One method of preparation is that described in U.S. Pat. No. 4,389,330. In this method the compound is dissolved or dispersed in an appropriate solvent. The polymeric matrix material is added to the compound containing medium in an amount relative to its desired loading. Optionally, all of the ingredients of the microparticle product can be blended in the solvent medium together.

Solvents for the compound and the polymeric matrix material that can be employed include organic solvents, such as acetone; halogenated hydrocarbons, such as chloroform, methylene chloride, and the like; aromatic hydrocarbon compounds, halogenated aromatic hydrocarbon compounds; cyclic ethers; alcohols, such as, benzyl alcohol; ethyl acetate; and the like.

The term "biodegradable" includes implants which comprise polymers which degrade by bodily processes to products readily disposable by the body and, advantageously, do not accumulate in the body. The products of the biodegradation should also be biocompatible with the body in the same sense that the polymeric matrix is biocompatible with the body. Suitable examples of biodegradable polymers include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate, and the like. Furthermore, some polymers may also be modified with end cap modifications such as alkyl caps. Such end caps are described in *Journal of Controlled Release* 52

(1998) 53–62 and *Journal of Controlled Release* 67 (2000) 281–292, the contents of each of which are incorporated herein by reference.

In a further embodiment, the polymer is selected so that it interacts with the N-phenyl substituted indolyl compound of formula (I) via ionic interactions. These interactions may retard the release of the compounds of the invention.

In one embodiment, the implant is comprised of a polymer that is biocompatible. The term "biocompatible" includes polymers which are not toxic to the human body, are not carcinogenic, and do not significantly induce inflammation in body tissues.

In one embodiment, the polymer comprises polylactide or a copolymer comprising polylactide such as dl(polylactide-co-glycolide). Examples of such biodegradable polymers include those which comprise about 30 to 100% polylactide and 0 to 70% polyglycolide. The copolymer and the compound of formula (I) may be fabricated into an implant via solvent casting and compression molding. In an embodiment, the individual polymers and the compound are dissolved in an organic solvent and solvent cast at a temperature at which the solvent evaporates for a period of time which allows for complete drying of the polymer-compound mixture. Complete drying can be assessed by weighing the material at the beginning of solvent casting and at the end of the solvent casting to ensure that all solvent has been evaporated. It may be noted that care should be taken to form a homogenous mixture to avoid the creation of macroscopic areas of high concentrations of the an N-phenyl substituted indolyl compound, which may result in "drug dumping."

In a further embodiment, the implants of the invention may further comprise a hydrophobic coating which may comprise one or more hydrophobic polymers. Examples of such hydrophobic polymers include PLGA, polycapralactone (PCL), PLA, ethylcellulose, and combinations and co-polymers thereof (including, but not limited to, PLGA-co-PCL and PLA-co-PCL). In a further embodiment, the hydrophobic polymers are selected to reduce water permeability of the implant and slow the release of the compound of the invention.

The N-phenyl substituted indolyl compound of formula (I) concentrations may range from about 5% to about 95%, from about 10% to about 80%, from about 20% to about 60%, or from about 30% to about 50% in the implant depending upon the release period.

The term "subject" includes animals (*e.g.*, mammals, *e.g.*, cats, dogs, horses, pigs, cows, sheep, rodents, rabbits, squirrels, bears, primates (*e.g.*, chimpanzees, gorillas, and humans)) which are capable of (or currently) suffering from a pyschiatric state. It also includes transgenic animal models. In a further embodiment, the subject is a human suffering from schizophrenia.

The term "treated," "treating" or "treatment" includes therapeutic and/or prophylactic treatment of a psychiatric state. The treatment includes the diminishment or alleviation of at least one symptom associated or caused by the psychiatric state. For example, treatment can be diminishment of one or several symptoms of the psychiatric state or complete eradication of the state.

In a further embodiment, the subject is treated for schizophrenia. The term treating may include the amelioration, correction, elimination, or reduction of one or more positive or negative symptoms of schizophrenia.

The language "the negative symptoms of schizophrenia" include a class of symptoms of schizophrenia which can be considered to reflect a `loss` in functional, directed thought or activity. Negative symptoms of schizophrenia include affective flattening (characterized by, for example, an immobile and/or unresponsive facial expression, poor eye contact and reduced body language), alogia (`poverty of speech` or brief, laconic and/or empty replies), avolition (characterized by a reduced or absent ability to initiate and carry out goal-directed activities), anhedonia (loss of interest or pleasure), social withdrawal, apathy and other negative symptoms known to those of skill in the art. The negative symptoms of schizophrenia may be assessed using any methodology known in the art including, but not limited to, the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Symptom Scale (PANSS), the Rorschach Schizophrenia Index (SCZI), and the Scale for the Assessment of Negative Symptoms (SANS). Some of these methods may also be used to assess positive symptoms (e.g., BPRS, PANSS and SCZI), although methods for specifically assessing positive symptoms are also available (e.g., the Scale for the Assessment of Positive Symptoms, or PANS).

The language "effective amount" of a compound of formula (I) is that amount necessary or sufficient to treat or prevent a psychiatric state in a subject, *e.g.* prevent the various morphological and somatic symptoms of a psychiatric state in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, or the type of illness. For example, the choice of the compound of formula (I) or salt can affect what constitutes an "effective amount".

The term "effective amount" also includes the amount of a compound of formula (I), e.g., sertindole, that will render a desired therapeutic outcome, e.g., a level or amount effective to reduce symptoms of a disorder. In a further embdoiment, the effective amount may be the effective amount to treat a psychiatric state such as schizophrenia and/or increase periods of therapeutic effectiveness ("on" periods). An amount that is "therapeutically effective" for a particular subject may depend upon such factors as a subject's age, weight, physiology, and/or the particular symptoms or condition to be treated, and will be ascertainable by a medical professional.

In a further embodiment, the effective amount of a compound of formula (I) is the amount necessary to achieve a plasma concentration of the compound of about 0.5 to about 100 ng/mL, of about 0.5 to about 90 ng/mL, of about 0.5 to about 80 ng/mL, of about 0.5 to about 70 ng/mL, of about 0.5 to about 60 ng/mL, of about 0.5 to about 50 ng/mL, 1 ng/ml to about 40 ng/ml, about 1 ng/ml to about-30 ng/ml, about 1 ng/ml to about 20 ng/ml, 1 ng/ml to about 15 ng/ml, or about 2.5 ng/ml to about 10 ng/ml. In a further embodiment, the effective amount is effective to maintain the aforementioned plasma concentration for at least one day or longer, one week or longer, two weeks or longer, three weeks or longer, four weeks or longer, six weeks or longer, two months or longer, three months or longer, four months or longer, five months or longer, six months or longer, seven months or longer, eight months or longer, nine months or longer, ten months or longer, eleven months or longer, twelve months or longer, or over a year or longer.

The term "administering" include surgically administering, implanting, inserting, or injecting the implant (or sections thereof) into a subject. The implant (or section) can be located subcutaneously intramuscularly, or located at another body location which allow the implant to perform its intended function. Generally, implants (or sections) are administered by subcutaneous implantation at sites including, but not limited to, the upper arm, back, or abdomen of a subject. Other suitable sites for administration may be readily determined by a medical professional. Multiple implants or sections may be administered to achieve a desired dosage for treatment.

In another embodiment, the invention pertains to a biodegradable implant, comprising a compound of formula (I), e.g., sertindole, and a biodegradable polymer. In a further embodiment, the implant comprises an effective amount of the compound of formula (I) to treat a disorder, e.g., a psychiatric disorder such as schizophrenia.

In a further embodiment, the compound of formula (I) is present in an amount in the implant which is effective to maintain an effective plasma level of the compound. In a further embodiment, the effective plasma level is at least 1 ng/ml for at least one day, one week, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months or twelve months or longer. In a further embodiment the plasma level of the compound of formula (I) is between about 1 ng/ml and about 100 ng/ml, about 1 ng/ml and about 90 ng/ml, about 1 ng/ml and about 80 ng/ml, about 1 ng/ml and about 70 ng/ml, about 1 ng/ml and about 60 ng/ml, about 1 ng/ml and about 50 ng/ml, about 1 ng/ml and about 40 ng/ml, about 1 ng/ml and about 30 ng/ml, about 1 ng/ml and about 20 ng/ml, or about 1 ng/ml and about 10 ng/ml.

In another embodiment, the invention also includes a method for maintaining an effective plasma level of the compound of formula (I) in a subject. The method includes administering to the subject an implant comprising a biodegradable polymer and a compound of formula (I), such that the plasma level of the compound is maintained for at least one day. In a further embodiment, the effective amount is between about 1 ng/ml and about 100 ng/ml, about 1 ng/ml and about 90 ng/ml, about 1 ng/ml and about 80 ng/ml, about 1 ng/ml and about 70 ng/ml, about 1 ng/ml and about 60 ng/ml, 1 ng/ml and about 50 ng/ml, about 1 ng/ml and about 40 ng/ml, about 1 ng/ml and about 30 ng/ml, about 1 ng/ml and about 20 ng/ml, or about 1 ng/ml and about 10 ng/ml. In another embodiment, the plasma levels are maintained for at least one day, one week, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months or twelve months or longer.

The invention also pertains to methods comprising administering second agents in combination with the biodegradable implants of the invention. The second agents may be any agent which enhances or increases the effectiveness of the treatment of the disorder (such as, but not limited to, psychiatric disorders) and/or reduce inflammation at the site of administration of the biodegradable implant, or which prevents or retards oxidation of the compound of formula (I). For example, an anti-inflammatory agent, such as for example, a steroid (e.g., dexamethasone, triamcinolone, betamethasone, clobetasol, cortisone, hydrocortisone, or a pharmaceutically acceptable salt thereof), or a nonsteroidal anti-inflammatory agent ("NSAID"; e.g., diclofenac potassium diclofenac sodium, diclofenac sodium with misoprostol, diflunisal, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, tolmetin, COX-2 inhibitors (e.g., celecoxib, rofecoxib, valdecoxib), acetylated salicylates (e.g., aspirin), nonacetylated salicylates (e.g., choline, magnesium, and sodium salicylates, salicylate)), and/or an antihistamine (e.g., loratadine ("LT"), astemizole, cetrizine dihydrochloride, chlorpheniramine, dexochlorpheniramine, diphenhydramine, mebhydrolin napadisylate, pheniramine maleate, promethazine, or terfenadine). The second agents may be encapsulated within the biodegradable implant to prevent or reduce local inflammation at the site of administration. The second agents may also be administered separately to the subject by any route that allows the second agents to perform their intended functions. The second agents may be administered orally, parentally, topically, subcutaneously, sublingually, etc. Any of the second agents, or a combinations thereof, may also be included in the same implant(s) as the compound of formula (I) or alternatively, may be incorporated into one or more separate implants or sections thereof that do not include the compound of formula (I). An

antioxidant, e.g., ascorbic acid, sodium metabisulfite, glutathione, may be included in the same implant or section thereof as the compound of formula (I) to prevent or reduce oxidation of the compound of formula (I) during preparation, storage, and/or administration of the implant or section thereof.

In a further embodiment, the invention also includes a method for treating a subject for schizophrenia, comprising administering to the subject a biodegradable implant, wherein the implant comprises an effective amount of a compound of formula (I), such as sertindole, to treat schizophrenia.

The implants (and sections thereof) can be manufactured using methods known in the art. For implants comprised of polymers that are viscose liquids at processing temperatures of 60-80 °C (e.g., polycapralactone and the like), the polymer is melted in an oven and the compound of formula (I) is mixed into the molten polymer with an electric mixer. The homogenous mixture of the compound of formula (I) and the polymer is then formed into implants by pouring it into molds, and/or by compression molding and/or extrusion.

For implants (or sections thereof) comprised of polymers that require pressure to flow at processing temperature, the compound of formula (I) and the polymer are melt mixed in a single or twin screw mixer/extruder that heats and kneads the drug and polymer prior to extrusion. The implants (or sections thereof) are then formed by extrusion alone or in combination with compression molding.

Pharmaceutically acceptable acid addition salts of the free bases of formula I are also part of this invention. The salts are prepared by methods well known to the art and are formed with both inorganic or organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methane sulfonic, ethane disulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids. The hydrohalic salts may be conveniently used.

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, *etc.*), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, *etc.*), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon

atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, *e.g.*, with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids.

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxophenyl, quinoline, isoquinoline, naphthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with

alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (*e.g.*, tetralin).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (*e.g.*, ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, *etc.*), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, *etc.*), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon

backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, *etc.*

The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "alkyl amino" includes groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively.

The term "amide" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

The term "hydroxy" or "hydroxyl" includes groups with an –OH or –O$^-$.

The term "halogen" includes fluorine, bromine, chlorine, iodine, *etc.* The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

The term "cyclic" includes saturated or unsaturated, aromatic or non-aromatic ring moieites. Examples of saturated cyclic moieties include piperidine, piperazine, morpholine, cyclohexyl, cyclobutyl, cyclopentyl, etc.

Exemplification of the Invention:

Example 1: Implant Fabrication

Implants are fabricated through solvent casting and compression molding. Three polymers, 85% polylactide with 15% polyglycolide (85:15 PLGA), 65% polylactide with 35% polyglycolide (65:35 PLGA), and 50% polylactide with 50% polyglycolide (50:50 PLGA) are present in a combined system of release during a 5-month period. Each copolymer has a distinctive period of degradation, which is determined by the ratio of lactide to glycolide and the molecular weight of the resulting molecule produced. An additional polymer of polycaprolactone/polylactide (PCL/PLA) is used for *in vivo*

testing in rats. Individual polymers and sertindole are dissolved in acetone and solvent cast at 60 °C for up to 14 days. Solvent cast material are compression molded at 80 ° and 25,000 psi (density 1.1.+-.0.05 grams/cc).

Example 2: *In vitro* Assay

Individual implants are placed in 1 liter of phosphate buffered saline (PBS), pH 7.4at 37 °C in constant motion. Sertindole amounts are measured by GCMS. Each assay includes negative controls of implants made of polymer alone and a 100 ng/ml sertindole standard to assess stability of sertindole in solution over time. The assay is also repeated using the same procedure at pH 4.4.

Example 3: *In vivo* Rodent Assay

Implants are also tested in rats (n=9) and mice (n=16). Animals are maintained with a 12:12 light:dark cycle with all testing and procedures performed during the light cycle.

Mice and rats are anesthetized with ketamine/xylazine (100/10 mg/kg, i.p.). A 1-cm incision is made in the skin on the dorsal aspect of the animal and an implant is placed between dermis and muscle. Removal of implants is performed with identical anesthesia and incision followed by implant retrieval.

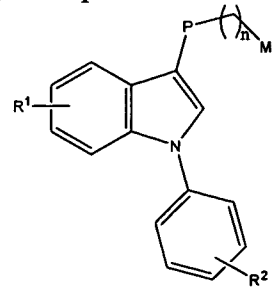
Bioactivity of sertindole implants are assessed in mice and rats. The mice received implants made of 85:15 PLGA, 65:35 PLGA, 50:50 PLGA or PCL alone or with 35% or 45% sertindole to assess the effects of implants. Following three weeks of implantation, the rats and mice are assessed for improvement. Implants are then removed and animals are allowed to recover for 48 hours prior to additional testing.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of the present invention and are covered by the following claims. The contents of all references, patents, and patent applications cited throughout this application are hereby incorporated by reference. The appropriate components, processes, and methods of those patents, applications and other documents may be selected for the present invention and embodiments thereof.

CLAIMS

1. A method for treating a subject for a disorder, comprising administering to said subject a biodegradable implant, wherein said implant comprises an effective amount of a N-phenyl substituted indolyl compound of formula (I):



(I)

wherein:

R^1 and R^2 are each independently hydrogen, halogen, hydroxyl, amino, thio, nitro, alkyl, alkenyl, aryl, cyano or alkynyl;

P is a saturated substituted or unsubstited cyclic moiety;

n is 0, 1, 2, or 3;

M is a substituted or unsubstituted heterocycle; or a pharmacuetically acceptable salt thereof, such that said subject is treated for said disorder.

2. The method of claim 1, wherein said disorder is associated with serotonin receptors.

3. The method of claim 1, wherein said disorder is a psychiatric state.

4. The method of claim 3, wherein said psychiatric state is a somatoform disorder, anxiety disorder, dissociative disorder, mood disorder, personality disorder, psychosexual disorder, schizophrenia, drug abuse and dependence, or a eating disorder.

5. The method of claim 4, wherein said psychiatric state is schizophrenia.

6. The method of any one of claims 1-5, wherein R^1 and R^2 are each independently halogen.

7. The method of claim 6, wherein R^1 is chlorine and R^2 is fluorine.

8. The method of any one of claims 1-7, wherein P is a saturated heterocyclic moeity.

9. The method of any one of claims 1-8, wherein n is 2.

10. The method of any one of claims 1-9, wherein M comprises one or more nitrogen atoms and/or carbonyl moieties.

11. The method of claim 10, wherein M is imidazolidin-2-one.

12. The method of any one of claims 1-5, wherein said compound is sertindole.

13. The method of any one of claims 1-12, wherein said effective amount results in a plasma level of said compound between about 1 ng/mL and about 40 ng/mL in said subject for at least one day.

14. The method of any one of claims 1-13, wherein said plasma level of said compound in said subject is maintained for at least one week.

15. The method of claim 14, wherein said plasma level is maintained for at least one month.

16. The method of claim 15, wherein said plasma level is maintained for at least three months.

17. The method of claim 16, wherein said plasma level is maintained for at least six or more months.

18. The method of anyone of claims 1-17, wherein said polymer comprises poly(glycolic acid), poly-D,L-lactic acid, poly-L-lacic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, natural polymers, or mixtures thereof.

19. The method of claim 18, wherein said natural polymer is albumin, casein, or a wax.

20. The method of any one of claims 1-19, wherein said polymer is charged.

21. The method of claim 18, wherein said polymer is a polyglycolide/polylactide co polymer or polycaprolactone.

22. The method of any one of claims 1-21, wherein said implant comprises one or more sections.

23. The method of claim 22, wherein said implant comprises two or more sections.

24. The method of claim 23, wherein said sections have different rates of degradation.

25. The method of any one of claims 1-24, wherein said implant comprises microparticles.

26. The method of claim 25, wherein said microparticles are injected in said subject.

27. The method of claim 25, wherein said microparticles are less than 500 μm in diameter.

28. The method of any one of claims 1-24, wherein said implant is removable.

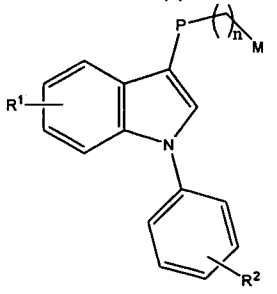
29. The method of any one of claims 1-24, wherein said implant has a diameter of at least about 1 mm.

30. The method of any one of claims 1-29, wherein at least one symptom of schizophrenia is treated.

31. The method of any one of claims 1-30, wherein said implant further comprises a hydrophobic coating.

32. The method of claim 31, wherein said hydrophobic coating is PLGA, PCL, PLA, ethylcellulose, or a combinations or copolymers thereof.

33. A biodegradable implant, comprising a biodegradable polymer and a N-phenyl substituted indolyl compound of formula (I):



(I)

wherein:

R^1 and R^2 are each independently hydrogen, halogen, hydroxyl, amino, thio, nitro, alkyl, alkenyl, aryl, cyano or alkynyl;

P is a saturated substituted or unsubstited cyclic moiety;

n is 0, 1, 2, or 3;

M is a substituted or unsubstituted heterocycle; or a pharmacuetically acceptable salt thereof.

34. The implant of claim 33, wherein R^1 and R^2 are each independently halogen.

35. The implant of claim 33 or 34, wherein R^1 is chlorine and R^2 is fluorine.

36. The implant of any one of claims 33-35, wherein P is a saturated heterocyclic moeity.

37. The implant of any one of claims 33-36, wherein n is 2.

38. The implant of any one of claims 33-37, wherein M comprises one or more nitrogen atoms and/or carbonyl moieties.

39. The implant of claim 33-38, wherein M is imidazolidin-2-one.

40. The implant of claim 39, wherein said compound is sertindole.

41. The implant of anyone of claims 33-40, wherein said polymer comprises poly(glycolic acid), poly-D,L-lactic acid, poly-L-lacic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, natural polymers, or mixtures thereof.

42. The implant of claim 41, wherein said polymer is a polyglycolide/polylactide co polymer or polycaprolactone.

43. The implant of any one of claims 33-42, wherein said compound is present in an amount which is effective to treat a disorder.

44. The implant of claim 43, wherein said disorder is associated with serotonin and/or serotonin receptors.

45. The implant of claim 43, wherein said disorder is a psychiatric state.

46. The implant of claim 45, wherein said psychiatric state is a somatoform disorder, anxiety disorder, dissociative disorder, mood disorder, personality disorder, psychosexual disorder, schizophrenia, drug abuse and dependence, or a eating disorder.

47. The implant of claim 46, wherein said psychiatric state is schizophrenia.

48. The implant of any one of claims 33-47, wherein said compound is present in an amount which is effective to maintain a compound level of between about 1 ng/ml and about 70 ng/ml in a subject for at least one day.

49. The implant of claim 48, wherein said compound levels are maintained for at least one week.

50. The implant of claim 49, wherein said compound levels are maintained for at least one month.

51. The implant of claim 50, wherein said compound levels are maintained for at least three months.

52. The implant of any one of claims 33-51, wherein said implant comprises microparticles.

53. The implant of claim 52, wherein said microparticles are less than 500 μm in diameter.

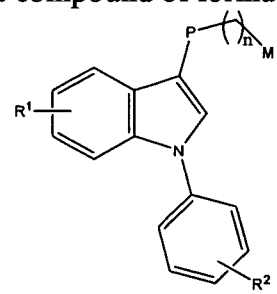
54. The implant of any one of claims 33-51, wherein said implant is removable.

55. The implant of any one of claims 33-51, wherein said implant has a diameter of at least about 1 mm.

56. The implant of any one of claims 33-55, wherein said implant further comprises a hydrophobic coating.

57. The implant of claim 56, wherein said hydrophobic coating is PLGA, PCL, ethylcellulose, or combination or a copolymer thereof.

58. A method for maintaining a plasma level of between about 1 and 70 ng/ml of a N-phenyl substituted indolyl compound of formula (I) in a subject, comprising administering to said subject an implant comprising a biodegradable polymer and said compound of formula (I), such that the plasma level of said compound is maintained for at least one day, wherein said compound of formula (I) is:



(I)

wherein:

R^1 and R^2 are each independently hydrogen, halogen, hydroxyl, amino, thio, nitro, alkyl, alkenyl, aryl, cyano or alkynyl;

P is a saturated substituted or unsubstited cyclic moiety;

n is 0, 1, 2, or 3;

M is a substituted or unsubstituted heterocycle; or a pharmacuetically acceptable salt thereof.

59. The method of claim 58, wherein said plasma level is maintained for at least one month.

60. The method of claim 59, wherein said plasma level is maintained for at least three months.

61. The method of any one of claims 58-60, wherein said subject is suffering from a disorder associated with serotonin and/or serotonin receptors.

62. The method of any one of claims 58-61, wherein said subject is suffering from a psychiatric state.

63. The method of claim 62, wherein said subject is suffering from a somatoform disorder, anxiety disorder, dissociative disorder, mood disorder, personality disorder, psychosexual disorder, schizophrenia, drug abuse and dependence, or a eating disorder.

64. The method of claim 63, wherein said psychiatric state is schizophrenia.

65. The method of any one of claims 58-64, wherein said compound is sertindole.

66. The method of anyone of claims 58-65, wherein said polymer comprises poly(glycolic acid), poly-D,L-lactic acid, poly-L-lacic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, natural polymers, or mixtures thereof.

67. The method of claim 66, wherein said polymer is a polyglycolide/polylactide co polymer or polycaprolactone.

68. The method of any one of claims 58-65, wherein said implant further comprises a hydrophobic coating.

69. The method of claim 68, wherein said hydrophobic coating is PLGA, PCL, PLA, ethylcellulose, or a combination or copolymer thereof.

70. A method for treating a subject for schizophrenia, comprising administering to said subject a biodegradable implant, wherein said implant comprises an effective amount of sertindole to treat schizophrenia.

71. A biodegradable implant, comprising sertindole and a biodegradable polymer.

72. The implant of claim 71, wherein said implant further comprises a hydrophobic coating.

73. The implant of claim 72, wherein said hydrophobic coating is PLGA, PCL, PLA, ethylcellulose, or combination or a copolymer thereof.