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(54) **INFRARED THERMOGRAPHY AND TREATMENT OF SEXUAL DYSFUNCTIONS**

INFRAROTTHERMOGRAPHIE UND BEHANDLUNG VON SEXUELLEN DYSFUNKTIONEN

THERMOGRAPHIE INFRAROUGE ET TRAITEMENT DE DYSFONCTIONNEMENTS SEXUELS

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US-A- 5 860 922 **US-A- 5 877 216**

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Description

[0001] This application claims priority to U.S. Provisional Application No. 60/202,935 filed May 9, 2000.

FIELD OF THE INVENTION

[0002] The present invention describes novel nitrosothio derivatives, useful for treating sexual dysfunctions, pharmaceutical compositions comprising them, their use in the manufacture of a medicament for treating sexual dysfunctions kits comprising them, and intermediates obtained in processes for their preparation.

BACKGROUND OF THE INVENTION

[0003] Adequate sexual function is a complex interaction of hormonal events and psychosocial relationships. There are four stages to sexual response as described in the International Journal of Gynecology & Obstetrics, 51(3):265-277 (1995). The first stage of sexual response is desire. The second stage of sexual response is arousal. Both physical and emotional stimulation may lead to breast and genital vasodilation and clitoral engorgement (vasocongestion). In the female, dilation and engorgement of the blood vessels in the labia and tissue surrounding the vagina produce the "orgasmic platform," an area at the distal third of the vagina where blood becomes sequestered. Localized perivaginal swelling and vaginal lubrication make up the changes in this stage of sexual response. Subsequently, ballooning of the proximal portion of the vagina and elevation of the uterus occurs. In the male, vasodilation of the cavemosal arteries and closure of the venous channels that drain the penis produce an erection. The third stage of sexual response is orgasm, while the fourth stage is resolution. Interruption or absence of any of the stages of the sexual response cycle can result in sexual dysfunction. One study found that 35% of males and 42% of females reported some form of sexual dysfunction. Read et al, J. Public Health Med., 19(4):387-391 (1997).

[0004] While there are obvious differences in the sexual response between males and females, one common aspect of the sexual response is the erectile response. The erectile response in both males and females is the result of engorgement of the erectile tissues of the genitalia with blood which is caused by the relaxation of smooth muscles in the arteries serving the genitalia. This increase in blood now results in vasodilation and an increase in the temperature of the genitalia tissue.

[0005] WO 00/25776, which is state of the art pursuant to Art. 54(3) and (4) EPC, discloses nitrosylated compounds and their use in therapy for treating, among others, inflammation, pain and fever.

[0006] WO 01/45703, which is state of the art pursuant to Art. 54(3) and (4) EPC, discloses NO donating agents and their use in therapy for treating, among others, male and female sexual dysfunctions.

[0007] US-A-5 877216 discloses the use of vasodilating agents such as S nitroso glutathione for treating sexual dysfunctions.

[0008] WO 97/27749 discloses the use of S nitrosothiol derivatives for treating male impotence.

SUMMARY OF THE INVENTION

[0009] One aspect of the present invention describes novel nitrosothio derivatives being a compound selected from 4-aza-4-(2-methyl-2-(nitrosothio)propyl)-tricyclo (5.2.1.0<2,6>)dec-8-ene-3,5-dione or a pharmaceutically acceptable salt thereof; and 4-(1-methyl-1-(nitrosothio) ethyl)-1,3-oxazolidin-2-one or a pharmaceutically acceptable salt thereof.

[0010] Another aspect of the invention provides a composition comprising the nitrosothio derivatives and a pharmaceutically acceptable carrier.

[0011] Yet another aspect of the invention provides the use of the composition in the manufacture of a medicament for treating a sexual desire disorder, a sexual arousal dysfunction, an orgasmic dysfunction or a sexual pain disorder.

[0012] Yet another aspect of the invention provides a kit comprising one or more containers filled with at least one of the nitrosothio derivatives.

[0013] Yet another aspect of the invention provides intermediates as produced in preparing the nitrosothio derivatives, being a compound selected from 4-aza-4-(2-methyl- 2- sulfanylpropyl) tricyclo-(5.2.1.0<2,6>) dec- 8-ene-3,5-dione or a pharmaceutically acceptable salt thereof; 4-{1-methyl-1-((2,4,6-trimethoxyphenyl)methylthio)ethyl}-1,3-oxazolidin-2-one or a pharmaceutically acceptable salt thereof; and 2-amino-3-methyl-3-((2,4,6-trimethoxyphenyl)methylthio)butan-1-ol-or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0014] **Fig. 1** shows the infrared thermographic images following topical administration of Example 1 (top panels) or vehicle (bottom panels) to a rabbit vagina and clitoris. The x axis corresponds to time in minutes from just prior to application of Example 1 or vehicle (0 minutes) to 60 minutes after application of Example 1 or vehicle. The vertical bar on the left hand side corresponds to the color change for temperatures ranging from 30 °C to 36 °C.

[0015] **Fig. 2** shows the infrared thermographic images following topical administration of 10% Example 2 (top panels) to rabbit vagina and clitoris. The x axis corresponds to time in minutes from just prior to application of Example 2 (0 minutes) to 60 minutes after application of Example 2. The bottom panels show the effect of administration of 10% phenylephrine (PE 10%, first bottom panel). The x axis corresponds to time in minutes for 5 minutes after the application of phenylephrine from 61 minutes to 65 minutes. The vertical bar on the left hand

side corresponds to the color change for temperatures ranging from 26 °C to 38 °C.

DETAILED DESCRIPTION OF THE INVENTION

[0016] As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

[0017] "Patient" refers to animals, preferably mammals, more preferably humans, and includes children and adults, and males and females..

[0018] "Infrared thermography" refers to the recording of the temperature of a body by means of infrared radiation emitted by the surface of the body at wavelengths of between about 0.8 μm and about 1 mm. The monitoring of radiation is preferably in the range of about 3 μm to about 100 μm, more preferably in the range of about 3 μm to about 15 μm, and most preferably in the range of about 3 μm to about 12 μm.

[0019] "Area of interest" refers to the area whose temperature is recorded and monitored using infrared thermography. The area of interest may include the symptomatic area.

[0020] "Baseline temperature" refers to the temperature of the area of interest at rest i.e., without the administration of a compound. The baseline temperature can be measured at, for example, prior to the administration of the test compound i.e., nitric oxide donor and/or vasoactive agent. Alternatively, the baseline temperature can be measured after the administration of the nitric oxide donor and/or vasoactive agent when a stable temperature reading is obtained.

[0021] "Raynaud's syndrome" refers to a condition that causes a loss of blood flow to the fingers, toes, nose and/or ears. The affected area turns white from the lack of circulation, then blue and cold, and finally numb. The affected area may also turn red, and may throb, tingle or swell.

[0022] "Gastrointestinal disorder" refers to any disease or disorder of the upper gastrointestinal tract of a patient including, for example, inflammatory bowel disease, peptic ulcers, stress ulcers, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, short-bowel (anastomosis) syndrome, hypersecretory states associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia, and bleeding peptic ulcers that result, for example, from neurosurgery, head injury, severe body trauma or burns.

[0023] "Upper gastrointestinal tract" refers to the esophagus, the stomach, the duodenum and the jejunum.

[0024] "Ulcers" refers to lesions of the upper gastrointestinal tract lining that are characterized by loss of tissue. Such ulcers include gastric ulcers, duodenal ulcers and gastritis.

[0025] "Therapeutically effective amount" refers to the amount of the compound and/or composition that is effective to achieve its intended purpose.

[0026] "Topical" refers to the delivery of a compound by passage through the skin and into the blood stream and includes transdermal delivery.

[0027] "Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

[0028] "Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

[0029] "Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

[0030] "Vaginal delivery" refers to the direct administration of a pharmaceutical composition to the vagina of the patient. Generally, "vaginal delivery" of a pharmaceutical composition involves administration to the distal several centimeters of the vagina.

[0031] "Vulvar delivery" or "vulvar administration" to refer to application of a pharmaceutical composition to the vulvar area of a patient. The term is intended to encompass application to the clitoris as well as the surrounding vulvar area. The terms "vulvar delivery" and "clitoral delivery" are used interchangeably herein and are both intended to refer to administration to the vulvar area of the patient

[0032] "Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

[0033] "Sustained release" refers to the release of a therapeutically active compound and/or composition such that the blood levels of the therapeutically active compound are maintained within a desirable therapeutic range over an extended period of time. The sustained release formulation can be prepared using any conventional method known to one skilled in the art to obtain the desired release characteristics.

[0034] The term "sexual dysfunction" generally includes any sexual dysfunction in a patient, including an animal, preferably a mammal, more preferably a human. The patient can be male or female. Sexual dysfunctions can include, for example, sexual desire disorders, sexual arousal disorders, orgasmic disorders and sexual pain disorders. Female sexual dysfunction refers to any female sexual dysfunction including, for example, sexual desire disorders, sexual arousal dysfunctions, orgasmic dysfunctions, sexual pain disorders, dyspareunia, and vaginismus. The female can be pre-menopausal or menopausal. Sexual dysfunction can be caused, for example, by pregnancy, menopause, cancer, pelvic surgery, chronic medical illness or medications. Male sexual dysfunction refers to any male sexual dysfunctions including, for example, male erectile dysfunction and impotence.

[0035] Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetraflurorborate in an inert solvent

[0036] Another embodiment of the present invention provides compositions comprising at least one nitrosothio derivative of the invention and at least one penetration enhancers that may be used to treat female sexual dysfunctions. The penetration enhancer, may preferably be a glyceride, such as, MIGLYOL®, and/or a polyglicolyzed glyceride, such as, LABROSOL® and/or LABROFIL®, or mixtures thereof.

[0037] In a particular embodiment, the glyceride penetration enhancer MIGLYOL® is MIGLYOL® 812N obtained from Condea Vista Company, Houston, Texas. MIGLYOL® 812N is a mixture of caprylic triglycerides and capric triglycerides. It can also contain decanoyl triglycerides, octanoyl triglycerides and C_8-C_{12} triglycerides.

[0038] The polyglycolyzed glyceride may be saturated or unsaturated and may include ethoxylated glycerides and polyethylene glycol esters. In a particular embodiment, the saturated polyglycolyzed glyceride is a glyceryl caprylate/caprate and PEG-8 (polyethylene glycol) caprylate/caprate complex known as LABRASOL® (Gattefosse Corp., New York). Suitable unsaturated polyglycolyzed glycerides are apricot kernel oil PEG-6 complex (LABRAFIL® M-1944 CS), almond oil PEG-6 complex (LABRAFIL® M-1966 CS), peanut oil PEG-6 complex (LABRAFIL® M-1969 CS), olive oil PEG-6 complex (LABRAFIL® M-1980 CS) and corn oil PEG-6 complex (LABRAFIL® M-2125 CS), all available from Gattefosse Corp., New York. Suitable ethoxylated glyceride, include C_8 -C_{10} carbon chain, for example glyceryl caprylate/caprate PEG-4 complex.

[0039] When administered *in vivo*, the nitrosothio derivatives of the present invention may be administered with pharmaceutically acceptable carriers and in dosages described herein. The nitrosothio derivatives of the present invention can also be used in combination with one or more additional compounds (e.g., therapeutic agents used to treat, diagnose and monitor the disease and disorder). The nitrosothio derivatives can be administered simultaneously with, subsequently to, or prior to administration of the other additional compound(s) to treat the diseases described herein.

[0040] The compounds and compositions of the present invention can be administered by any available and effective delivery system including orally, bucally, parenterally, by inhalation spray (oral or nasal), by topical application, by injection into the corpus cavemosum tissue, by transurethral drug delivery, vaginally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, and infusion techniques. Parenteral also includes injection into the corpus cavernosum tissue, which can be conducted using any effective injection system including conventional syringe-and-needle systems or needleless injection devices.

[0041] Solid dosage forms for oral administration can include capsules, tablets, effervescent tablets, chewable tablets, pills, powders, effervescent powders, sachets, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the present invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings.

[0042] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0043] Suppositories for vaginal or rectal administration of the compounds and compositions of the invention can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at body temperature, such that they will melt and release the drug.

[0044] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium.

[0045] Topical administration, which is well known to one skilled in the art, involves the delivery of pharmaceutical agents via percutaneous passage of the drug into

the systemic circulation of the patient. Topical administration includes vaginal administration, vulval administration, penile administration and rectal administration. Topical administration can also involve transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride.

[0046] Dosage forms for topical administration of the compounds and compositions of the present invention preferably include creams, sprays, lotions, gels, ointments, emulsions, coatings for condoms, liposomes, foams. Administration of the cream, spray, ointment, lotion, gel, emulsion, coating, liposome, or foam can be accompanied by the use of an applicator or by transurethral drug delivery using a syringe with or without a needle or penile insert or device, or by clitoral, vulval or vaginal delivery, and is within the skill of the art. Alternatively, the compositions may be contained within a vaginal ring, tampon, suppository, sponge, pillow, puff, or osmotic pump system; these platforms are useful solely for vaginal delivery. Typically a lubricant and/or a local anesthetic for desensitization can also be included in the formulation or provided for use as needed. Lubricants include, for example, K-Y jelly (available from Johnson & Johnson) or a lidocaine jelly, such as XYLOCAINE® 2% jelly (available from Astra Pharmaceutical Products). Local anesthetics include, for example, novocaine, procaine, tetracaine, benzocaine.

[0047] Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery. An ointment base should be inert, stable, nonirritating and nonsensitizing. Ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, semisolid hydrocarbons obtained from petroleum, and the like. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no welter and include, for example, hydroxystearin sulfate, anhydrous lanolin, hydrophilic petrolatum, and the like. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid, and the like In a particular embodiment, water-soluble ointment bases are preferred and are prepared from polyethylene glycols of varying molecular weight, and can be determined by standard techniques as described in Remington: The Science and Practice of Pharmacy.

[0048] Lotions are preparations that may be applied without friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and in a particular embodiment, may comprise a liquid oily emulsion of the oil-in water type. It is generally necessary that the insoluble matter in a lotion be finely divided. Lotions will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing the active agent in contact with the skin, such as, for example, methylcellulose, sodium carboxymethyl-cellulose.

[0049] Emulsion formulations are generally formed from a dispersed phase (for example., a pharmacologically active agent), a dispersion medium and an emulsifing agent. If desired, emulsion stabilizers can be included in the formulation as well. A number of pharmaceutically useful emulsions are known in the art, including, for example, oil-in-water (o/w) formulations, water-in-oil (w/o) formulations and multiple emulsions such as w/o/w or o/w/o formulations. Emulsifying agents suitable for use in such formulations include, but are not limited to, TWEEN 60®, SPAN 80®, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate.

[0050] Creams are, as known in the art, viscous liquid or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as, cetyl alcohol, stearyl alcohol, and the like; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant

[0051] The ointments, lotions, emulsions and creams are formed by dispersing finely divided or dissolved the nitrosothio derivative(s) uniformly throughout the vehicle or base using conventional techniques, typically by levigating the compound with a small quantity of the base to form a concentrate which is then diluted geometrically with further base. Alternatively, a mechanical mixer may be used. Creams, lotions and emulsions are formed by way of a two-phase heat system, wherein oil-phase ingredients are combined under heat to provide a liquified, uniform system. The aqueous-phase ingredients are separately combined using heat. The oil and aqueous phases are then added together with constant agitation and allowed to cool. At this point, concentrated agents may be added as a slurry. Volatile or aromatic materials can be added after the emulsion has sufficiently cooled. Preparation of such pharmaceutical compositions is within the general skill of the art. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (Easton, Pa: Mack Publishing Company, 1990).

[0052] The compounds and compositions of the present invention will typically be administered in a pharmaceutical composition containing one or more carriers or excipients, i.e., pharmaceutically acceptable organic

or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Examples of pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, silicone, waxes, petroleum jelly, vegetable oils, polyethylene glycols, propylene glycol, liposomes, sugars, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone.

[0053] The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents which do not deleteriously react with the active compounds, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

[0054] The pharmaceutical compositions may also include a detergent in the formulation, in an amount effective to increase solubility of the nitrosothio derivative in the vehicle and bioavailability of the agent following administration. The detergent will typically be a nonionic, anionic, cationic or amphoteric surfactant. The surfactant is selected such that local irritation at the site of administration is avoided. Surfactants include, for example, TERGITOL® and TRITON® surfactants (Union Carbide Chemicals and Plastics, Danbury, CN polyoxyethylene sorbitan fatty acid esters, e.g., TWEEN® surfactants (Atlas Chemical Industries, Wilmington, DE.), such as, for example, polyoxyethylene 20 sorbitan monolaurate (TWEEN® 20), polyoxyethylene (4) sorbitan monolaurate (TWEEN® 21), polyoxyethylene 20 sorbitan monopalmitate (TWEEN® 40), polyoxyethylene 20 sorbitan monooleate (TWEEN® 80, and the like; polyoxyethylene 4 lauryl ether (BRIJ® 30), polyoxyethylene 23 lauryl ether (BRIJ 35), polyoxyethylene 10 oleyl ether (BRIJ® 97); polyoxyethylene glycol esters, such as, for example, poloxyethylene 8 stearate (MYRJ® 45), poloxyethylene 40 stearate (MYRJ® 52) polyoxyethylene alkyl ethers, or mixtures thereof.

[0055] The pharmaceutical preparation may also include one or more permeation enhancers. Permeation enhancers include those generally useful in conjunction with topical, transdermal or transmucosal drug delivery. Permeation enhancers include, for example, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide (C_{10} MSO), polyethylene glycol monolaurate (PEGML), polyethyleneglycol, glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, such as, 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark AZONE® from Nelson Research & Development Co., Irvine, CA.), lower alkanols (e.g., ethanol), C_6 to C_{20} -hydrocarbyl substituted 1,3-dioxane, C_6 to C_{20} -hydrocarbyl substituted 1,3-dioxolane and C_6 to C_{20} -hydrocarbyl substituted acetal, such as, SEPA® (available from Macrochem Co., Lexington, MA.), alkonates, such as, alkyl-2-(N,N-disubstituted amino)-alkonate ester, N,N-disubstituted amino)-alkanol alkanoate, glycerides, such as mono, di and triglycerides and mixtures thereof such as for example MIGLYOL® (Condea Vista Company, Houston, TX) and the like; polyglycolyzed glycerides, such as, for example, LABRASOL® and LABRAFIL®, and the like; and surfactants as discussed above, including, for example, TERGITOL.® and TRITON® surfactants, NONOXYNOL-9® and TWEEN-80®. In particular embodiments the penetration enhancers may be MIGLYOL®, LABRASOL® or LABRAFIL®, including mixtures thereof.

[0056] In some cases, the formulations may include one or more compounds effective to inhibit enzymes present in the vaginal or vulvar areas which could degrade or metabolize the pharmacologically active agent.

[0057] Various delivery systems are known and can be used to administer the compounds or compositions of the present invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules. The required dosage can be administered as a single unit or in a sustained release form.

[0058] The bioavailabilty of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants. The bioavailability and absorption of the nitrosothio derivative can be increased by the addition of tabletting excipients, such as, for example β-cyclodextin, a β-cyclodextrin derivative, such as for example, hydroxypropyl-β-cyclodextrin (HPBCD), and the like. Inclusion complexes are complexes formed by interaction of macrocyclic compounds containing an intramolecular cavity of molecular dimensions with the smaller, pharmacologically active agent. Preferred inclusion complexes are formed from α-, β- and γ-cyclodextrins, or from clathrates, in which the "host" molecules form a crystal lattice containing spaces in which "guest" molecules (i.e., in this case, the nitrosothio derivative) will fit. See, e.g., Hagan, Clathrate Inclusion Compounds (New York: Reinhold, 1962).

[0059] Liposomes are microscopic vesicles having a lipid wall comprising a lipid bilayer, and can be used as drug delivery systems as well. Generally, liposome formulations are preferred for poorly soluble or insoluble pharmaceutical agents. Liposomal preparations for use in the pressent invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. Cationic liposomes are readily available. For example, N(1-2,3-dioleyloxy) propyl)-N,N,N-triethylammonium (DOTMA) liposomes are available under the

tradename LIPOFECTIN® (GIBCO BRL, Grand Island, N.Y.). Similarly, anionic and neutral liposomes are readily available as well, from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE).

[0060] These materials can also be mixed with DOTMA in appropriate ratios. Methods for making liposomes using these materials are well known in the art See Remington's Pharmaceutical Sciences, supra.

[0061] The release of the nitrosothio derivative can be controlled by dissolution (bioerosion) of a polymer using either encapsulated dissolution control or matrix dissolution control. In encapsulated dissolution control, the derivative is coated with a membrane of slowly dissolving polymeric or wax materials. When the encapsulating membrane has dissolved, the agent core is available for immediate release and adsorption across the epithelial or mucosal surfaces of the vagina or vulvar area. Bioerodible coating materials may be selected from a variety of natural and synthetic polymers, depending on the agent to be coated and the desired release characteristics. Exemplary coating materials include gelatins, carnauba wax, shellacs, ethylcellulose, cellulose acetate phthalate, cellulose acetate butyrate, and the like. Release of the compound is controlled by adjusting the thickness and dissolution rate of the polymeric membrane. A uniform sustained release can be attained by compressing a population of particles of the agent with varying membrane thickness (e.g., varying erosion times) into a tablet form for a single administration.

[0062] In matrix dissolution control, the nitrosothio derivative is dissolved or dispersed within a matrix of, such as, for example, an erodible wax. The compound is released for adsorption across the epithelial or mucosal surfaces of the vagina or vulvar area as the matrix bioerodes. The rate of compound availability is generally controlled by the rate of penetration of the dissolution media (i.e., vaginal fluids) into the matrix, wherein the rate of penetration is dependent on the porosity of the matrix material. Bioerodible matrix dissolution delivery systems can be prepared by compressing the nitrosothio derivative with a slowly soluble polymer carrier into a tablet or suppository form. There are several methods of preparing drug/wax particles including congealing and aqueous dispersion techniques. In congealing methods, the derivative is combined with a wax material and either spray-congealed, or congealed and then screened. For an aqueous dispersion, the derivative wax combination is sprayed or placed in water and the resulting particles collected. Matrix dosage formulations can be formed by compaction or compression of a mixture of nitrosothio derivative, polymer and excipients.

[0063] In an alternative embodiment, the compositions of the present invention may be administered as biodegradable adhesive film or sheet which adhere to the vulvar area. Such drug delivery systems are generally composed of a biodegradable adhesive polymer based on a polyurethane, a poly(lactic acid), a poly(glycolic acid), a poly(ortho ester), a polyanhydride, a polyphosphazene, or a mixture or copolymer thereof. Preferred biodegradable adhesive polymers include, for example, polyurethanes and block copolyurethanes containing peptide linkages, simple mixtures of polyurethanes and polylactides, and copolymers of acrylates and mono- or disaccharide residues.

[0064] The compounds and compositions of the present invention can be formulated as pharmaceutically acceptable salts. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric (nitrate salt), nitrous (nitrite salt), carbonic, sulfuric and phosphoric acid and the like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example; formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesuifonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

[0065] "Therapeutically effective amount" refers to the amount of the nitrosothio derivative which is effective to achieve its intended purpose. In preferred embodiments of the methods described herein, the nitrosothio derivatives are administered in a therapeutically effective amount. While individual patient needs may vary, determination of optimal ranges for effective amounts of each nitrosothio derivative is within the skill of the art. Generally the dosage regimen for monitoring and idagnosing a condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the dysfunction, the route of administration, pharmacological considera-

tions such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination and can be adjusted by one skilled in the art. Thus, the dosage regimen actually employed may vary from the preferred dosage regimen set forth herein.

[0066] The amount of a given nitriosothio derivative which will be effective in monitoring and diagnosing a particular dysfunction or condition will depend on the nature of the dysfunction or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, supra; The Physician's Desk Reference, supra; Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the dysfunction or disorder, and should be decided by the physician and the patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems and are in the same ranges or less than as described for the commercially available compounds in the Physician's Desk Reference, supra.

[0067] In particular embodiments the methods of administration of the nitrosothio derivatives for treating male sexual dysfunction are by oral administration, by topical application, by injection into the corpus cavernosum, by transurethral administration or by the use of suppositories. The preferred methods of administration for treating female sexual dysfunction are by oral administration, topical application or by the use of suppositories. The most preferred mode of administration for female sexual dysfunction is topical application, preferably as an ointment, a cream, a gel, an emulsion, a spray or a lotion. These compositions may contain at least one penetration enhancer to increase the permeability of the nitrosothio derivative across the membrane.

[0068] The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the present invention. Such kits can also include, for example, other compounds and/or compositions (e.g., permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflects approval by the agency of manufacture, use or sale for human administration

EXAMPLES

Example 1: 4-Aza-4-(2-methyl-2-(nitrosothio)propyl) tricyclo(5.2.1.0<2,6>)dec-8-ene-3,5-dione

1a. 4-Aza-4-(2-methyl-2-sulfanylpropyl)tricyclo (5.2.1.0<2,6>)dec-8-ene-3,5-dione

[0069] A suspension of 1-amino-2-methylpropane-2-thiol hydrochloride (6.72 g, 47.4 mmol) in ethyl acetate (200 mL) was shaken with potassium hydroxide solution (16 M, 3.6 mL, 57.0 mmol). The ethyl acetate solution was separated, dried with sodium sulfate, filtered, and concentrated to give 1-amino-2-methylpropane-2-thiol (2.70 g, 25.7 mmol, 54%). The thiol was dissolved in acetic acid (25 mL) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (4.17 g, 25.4 mmol) was added. The reaction was stirred at 100 °C for 1 hour and allowed to stand at room temperature over the weekend. The crystals which formed were collected by filtration, washed with acetic acid (4 mL) and a small volume of methanol, and then dried in *vacuo* to give the title compound (2.22 g, 35 %). The filtrate was concentrated, treated with toluene and concentrated (repeat four times). The residue dissolved in dichloromethane and filtered through silica gel to give additional product (2.47 g) contaminated with a little *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride. ^{1}H NMR ($CDCl_3$) δ 6.16 (s, 2H), 3.52 (s, 2H), 3.42 (s, 2H), 3.32 (s, 2H), 1.86 (s, 1H), 1.76 (d, *J*=8.77 Hz, 1H), 1.57 (d, *J*=8.77 Hz, 1H), 1.30 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 177.9, 134.8, 52.5, 51.0, 45.8, 45.24, 45.0, 30.9. LRMS (APIMS) *m/z* 252 (MH^+).

1b. 4-Aza-4-(2-methyl-2-(nitrosothio)propyl)tricyclo (5.2.1.0<2,6>)dec-8-ene-3,5-dione

[0070] To a solution of Example 1a (793 mg, 3.156 mmol) in dichloromethane (23 mL) was added tert-butyl nitrite (750 μL, 650 mg, 6.31 mmol) and the solution was stirred at room temperature for 1 hour in the dark. The reaction mixture was concentrated and the residue chromatographed (ethyl acetate:hexane 2:3) to give the title compound (768.7mg, 2.738 mmol, 87 %). ^{1}H NMR ($CDCl_3$) δ 6.12 (s, 2H), 4.10 (s, 2H), 3.41 (s, 2H), 3.30 (s, 2H), 1.82 (s, 6H), 1.75 (d, *J*=8.8 Hz, 1H), 1.57 (d, *J*=8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 177.7, 134.7, 56.7, 52.4, 48.0, 47.0, 46.0, 45.8, 45.0, 27.5. LRMS (APIMS) *m/z* 298 (M^++NH_4), 99.3% purity by HPLC analysis (Column: Water μBondpack C18; Size: 3.9 mm x 150 mm; Solvent A: acetonitrile / 0.1% TFA; Solvent B: water / 0.1% TFA; Flow rate: 1.0 mL / min; Program 20% A to 95% A over 20 min.; Detection: 254 nm; Sample: 4.3 mg / mL; Injection volume: 10μ L).

Example 2: 4-(1-Methyl-1-(nitrosothio)ethyl)-1,3-ozazolidin-2-one

2a. 2-Amino-3-methyl-3-((2,4,6-trimethoxyghenyl)methylthio)butanoic acid

[0071] A suspension of 2-amino-3-methyl-3-sulfanylbutanoic acid (D-penicillamine) (5.0 g, 34 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C. Trifluoroacetic acid (54 mL,

703 mmol) was added dropwise over a period of 5 minutes. Then 2,4,6,-trimethoxybenzyl alcohol (6.64 g, 34 mmol) in CH_2Cl_2 (137 mL) was added dropwise at 0 °C with stirring. Stirring was continued for 1 hour at 0°C and 2 hours at room temperature. The solvent was removed *in vacuo* and the residue was dried under high vacuum for 3 hours. The crude red solid was recrystallized from 1:1:1 CHiCl2/MeOH/EtOAc to give the title compound as a white solid (10.5 g, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 2H), 3.84 (s, 6H), 3.76 (s, 3H), 3.40-4.10 (m, 3H), 1.69 (s, 3H), 1.23 (s, 3H). LRMS (EI) *m/z* 330 (MH^+).

2b. 2-Amino-3-methyl-3-((2,4,6-trimethoxyphenyl)methylthio)butan-1-ol

[0072] To a stirred solution of Example 2a (10.5 g, 32 mmol) in THF (80 mL) was added dropwise lithium aluminum hydride (1 M in THF, 64 mL, 64 mmol) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 1 hour and then at room temperature for 2 hours. The excess reducing agent was destroyed carefully by portionwise addition of Na. $_2SO_4$•$10H_2O$ at 0 °C. The granular white precipitate was filtered and washed with 30% methanol in CH_2Cl_2. The combined filtrates were dried over Na_2SO_4, filtered and evaporated to give the title compound as a yellow oil (7.6 g, 76 %) which was used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 2H), 3.85 (s, 6H), 3.81 (s, 3H), 3.74 (s, 2H), 3.60-3.80 (m, 2H), 3.37-3.43 (m, 1H), 2.93-2.98 (m, 1H), 1.45 (s, 3H), 1.30 (s, 3H). LRMS (EI) *m/z* 316 (MH^+).

2c. 4-{1-Methyl-1-((2,4,6-trimethoxyphenyl)memylthio) ethyl}-1,3-oxazolidin-2-one

[0073] A mixture of K_2CO_3 (0.33 g, 2.4 mmol), diethylcarbonate (50 mL) and the product of Example 2b (7.6 g, 24 mmol) was heated at 100 °C for 24 hours. The solvent was evaporated and the resultant light brown slurry was cooled to room temperature, diluted with CH_2Cl_2 and filtered to remove the K_2CO_3. The filtrate was evaporated and the residue was chromatographed on silica gel eluting with 1:1 EtOAc:Hex to give the title compound as a viscous yellow oil (2.6 g, 32 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (s, 2H), 6.07 (bs, 1H), 4.30-4.40 (m, 1H), 4.25-4.28 (m, 1H), 4.03-4.08 (m, 1H), 3.86 (s, 6H), 3.83 (s, 2H), 3.81 (s, 3H), 1.32 (s, 3H), 127 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 159.5, 158.7, 106.3, 90.9, 66.5, 59.5, 56.0, 55.5, 47.1, 23.8, 22.3, 20.3. LRMS (EI) *m/z* 342 (MH^+), 359 (MNH_4^+), 364 (MNa^+).

2d. 4-(1-Methyl-1-sulfanylethyl)-1,3-oxazolidin-2-one

[0074] The product of Example 2c (2.5 g, 7.3 mmol) was treated with water (2.9 mL), phenol (2.9 g), anisole (2.9 mL) and finally trifluoroacetic acid (36 mL). The resultant solution was stirred at room temperature for 1 hour and the solvent was evaporated to give a yellow oil. The yellow oil was dissolved in CH_2Cl_2, washed with saturated sodium bicarbonate, brine and dried over Na_2SO_4. The residue after filtration and evaporation of the solvent was chromatographed on silica gel eluting with 0.5:1:1 EtOAc:CH_2Cl_2:Hex to give the title compound as a white solid (0.94 g, 80%). mp 124-126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00-6.10 (bs, 1H), 4.30-4.50 (m, 2H), 3.80-3.84 (m, 1H), 1.69 (s, 1H), 1.36 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 67.3, 62.9, 46.4, 27.5, 27.4. LRMS (EI) *m/z* 162 (MH^+), 179 (MNH_4^+). Anal. Calcd for $C_6H_{11}NO_2S$• 1/6 EtOAc: C, 45.52; H, 7.07; N, 7.96 Found: C, 45.83; H, 6.86; N, 8.19.

2e. 4-(1-Methyl-1-(nitrosothio)ethyl)-1,3-oxazolidin-2-one

[0075] To a solution of tert-butyl nitrite (1.7 mL of 90% solution, 1.48 g, 14.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of Example 2d (0.94 g, 5.8 mmol) in CH_2Cl_2 (13 mL) at 0 °C. The resulting green solution was stirred at 0 °C for 20 minutes and then at room temperature for 15 minutes in the dark. The residue after evaporation of the solvent was chromatographed on silica gel eluting with 1:4 EtOAc:CH_2Cl_2 to give the title compound as a purple-green solid (0.89 g, 80%). mp 65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (bs, 1H), 4.40-4.65 (m, 3H), 1.94 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 67.0, 61.3, 58.1, 25.3, 24.0. LRMS (EI) *m/z* 191 (MH^+), 208 (MNH_4^+). Anal. Calcd for $C_6H_{10}N_2O_3S$: C, 37.89; H, 5.30; N, 14.73; S, 16.85. Found: C, 37.97; H, 5.26; N, 14.45; S, 16.78.

Example 3: Infrared thermographic measurements

[0076] Female white New Zealand rabbits were anaesthetized with pentobarbitol sodium and placed in a supine position on a warming pad. The warming pad was connected to a temperature control unit to maintain the core (rectal) temperature to 38°C. The labia and clitoris were exposed and kept in position by taping the surrounding skin to the nearby abdominal area. The infrared camera (THERMACAM® SC 1000, Inframetrics Inc., North Billerica, MA) was focused on the labia and clitoris and the animal was covered with a chamber to maintain the heat loss due to air movement

[0077] After a steady baseline temperature was maintained and recorded for at least 10 minutes the compound (50 μL) was applied to the surface of the labia and clitoris using a syringe and 27G needle. The compound was formulated in a mixture of dimethyl sulfoxide (25%) and poly(ethylene glycols) (75%). The poly(ethylene glycols) was a mixture of poly(ethylene glycol) 1450 and poly(ethylene glycol) 400 in a ratio of 1:9 respectively.

[0078] The images from the infrared camera were electronically transferred to a PC computer and analyzed using TherMonitor 95, version 1.61 (Thermoteknix System Ltd., Mount pleasant,Cambridge, U. K.). Various color scales in the visible wave length are used to depict the

temperature change of the recorded images.

Example 4: Infrared thermography measurements following topical administration of Example 1

[0079] Infrared thermographic measurements were recorded as described in Example 3. **Figs. 1** shows the temperature change of the rabbit genitalia following the topical administration of Example 1 (5%) or vehicle. As can be seen from **Fig. 1** (top panels), the temperature of the labia and clitoris changes from -32°C prior to the application of the compound to 35 °C following the application of Example 1. The application of the vehicle alone did not result in a temperature increase **Fig 1** (bottom panels).

Example 5: Infrared thermography measurements following topical administration of Example 2

[0080] Infrared thermographic measurements were recorded as described in Example 3. **Figs. 2** shows the temperature increase of the rabbit genitalia following the topical administration of Example 2 (10%). As can be seen from **Fig. 2** (top panel), the temperature of the labia and clitoris changes from ~32 °C prior to the application of the compound to 36 °C following the application of Example 2. After 60 minutes the vasoconstrictor, phenylephrine (10%), was applied and the temperature monitored for an additional 5 minutes. As can be seen from **Fig. 2** (bottom panels), the addition of the vasoconstrictor resulted in a decrease in the temperature from 36°C to 32 °C. The results show that the temperature changes can be used as a measure of vasodilation of the tissue.

Claims

1. A compound selected from 4-aza-4-(2-methyl-2-(nitrosothio) propyl)-tricyclo (5.2.1.0<2,6>) dec- 8- ene-3,5-dione or a pharmaceutically acceptable salt thereof; and 4-(1-methyl-1-(nitrosothio)ethyl)-1,3-oxazolidin-2-one or a pharmaceutically acceptable salt thereof.

2. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

3. The composition of claim 2, further comprising at least one penetration enhancer.

4. The composition of claim 3, wherein the penetration enhancer is dimethylsulfoxide, dimethyl formamide, N,N-dimethylacetamide, decylmethylsuffoxide, polyethylene glycol monolaurate, polyethyleneglycol, glycerol monolaurate, lecithin, a 1-substituted azacycloheptan-2-one, a lower alkanol, a C_6 to C_{20}-hydrocarbyl substituted 1,3-dioxane, a C_6 to C_{20}-hydrocarbyl substituted 1,3-dioxolane or a C_8 to C_{20}-hydrocarbyl substituted acetal, an alkonate, a glyceride, a surfactant, or a mixture thereof.

5. The composition of claim 4, wherein the glyceride is a mono glyceride, a diglyceride, a triglyceride, a polyglycolyzed glyceride or a mixture thereof.

6. The composition of claim 5, wherein the glyceride is a mixture of caprylic triglycerides and capric triglycerides, a decanoyl triglyceride, an octanoyl triglyceride, a C_8 - C_{12} triglyceride, a saturated polyglycolyzed glyceride, a glyceryl caprylate/caprate and PEG-8 (polyethylene glycol) caprylate/caprate complex, an unsaturated polyglycolyzed glyceride, an apricot kernel oil PEG-6 complex, an almond oil PEG-6 complex, a peanut oil PEG-6 complex, an olive oil PEG-6 complex, a corn oil PEG-6 complex, an ethoxylated glyceride, a glyceryl caprylate/caprate PEG-4 complex, or a mixture thereof.

7. Use of a composition of claim 2 in the manufacture of a medicament for treating a sexual desire disorder, a sexual arousal dysfunction, an orgasmic dysfunction or a sexual pain disorder.

8. The use of claim 7, wherein the patient is female.

9. The use of claim 7, wherein the patient is male.

10. The use of claim 7 wherein the composition is administered orally, bucally, topically, by injection, by inhalation spray or by transurethral application.

11. The use of claim 10, wherein the composition is administered orally as a solid or liquid dose.

12. A kit comprising one or more containers filled with at least one compound of claim 1.

13. The kit of claim 12, further comprising at least one penetration enhancer.

14. A compound selected from 4-aza-4-(2-methyl-2-sulfanylpropyl) tricyclo-(5.2.1.0<2.6>) dec- 8- ene- 3,5-dione or a pharmaceutically acceptable salt thereof; 4-{1-methyl-1-((2,4,6-trimethoxyphenyl)methylthio) ethyl}-1,3-oxazolidin-2-one or a pharmaceutically acceptable salt thereof; and 2-amino-3-methyl-3-((2,4,6-trimethoxyphenyl)methylthio)butan-1-ol or a pharmaceutically acceptable salt thereof.

15. 4- aza- 4-(2- methyl- 2-(nitrosothio) propyl) tricyclo (5.2.1.0<2,6>)dec-8-ene-3,5-dione or a pharmaceutically acceptable salt thereof.

16. 4-(1- methyl- 1-(nitrosothio) ethyl)- 1,3- oxazolidin- 2-one or a pharmaceutical acceptable salt thereof.

Patentansprüche

1. Verbindung ausgewählt aus 4-Aza-4-(2-methyl-2-(nitrosothio) propyl)-tricyclo (5.2.1.0<2,6>) dec- 8-en-3,5-dion oder einem pharmazeutisch verträglichen Salz davon; und 4-(1-Methyl-1-(nitrosothio) ethyl)-1,3-oxazolidin-2-on oder einem pharmazeutisch verträglichen Salz davon.

2. Zusammensetzung, umfassend die Verbindung nach Anspruch 1 und einen pharmazeutisch verträglichen Träger.

3. Zusammensetzung nach Anspruch 2, weiter umfassend mindestens ein Mittel zur Verbesserung der Penetrationsfähigkeit.

4. Zusammensetzung nach Anspruch 3, wobei das Mittel zur Verbesserung der Penetrationsfähigkeit Dimethylsulfoxid, Dimethylformamid, N,N-Dimethylacetamid, Decylmethylsulfoxid, Polyethylenglycolmonolaurat, Polyethylenglycol, Glycerinmonolaurat, Lecithin, ein 1-substituiertes Azacycloheptan-2-on, ein Niederalkanol, ein mit C_6-C_{20}-Hydrocarbyl substituiertes 1,3-Dioxan, ein mit C_6-C_{20}-Hydrocarbyl substituiertes 1,3-Dioxolan oder ein mit C_6-C_{20}-Hydrocarbyl substituiertes Acetal, ein Alkonat, ein Glycerid, ein oberflächenaktives Mittel oder ein Gemisch davon ist.

5. Zusammensetzung nach Anspruch 4, wobei das Glycerid ein Monoglycerid, ein Diglycerid, ein Triglycerid, ein polyglycolisiertes Glycerid oder ein Gemisch davon ist.

6. Zusammensetzung nach Anspruch 5, wobei das Glycerid ein Gemisch aus Caprylтriglyceriden und Caprintriglyceriden, ein Decanoyltriglycerid, ein Octanoyltriglycerid, ein C_8-C_{12}-Triglycerid, ein gesättigtes polyglycolisiertes Glycerid, ein Glycerylcaprylat/caprat und PEG-8 (Polyethylenglycol) Caprylat/Capratkomplex, ein ungesättigtes polyglycolisiertes Glycerid, ein Aprikosenkernöl-PEG-6-Komplex, ein Mandelöl-PEG-6-Komplex, ein Erdnussöl-PEG-6-Komplex, ein Olivenöl-PEG-6-Komplex, ein Maiskeimöl-PEG-6-Komplex, ein ethoxyliertes Glycerid, ein Glycerylcaprylat/caprat-PEG-4-Komplex oder ein Gemisch davon ist.

7. Verwendung einer Zusammensetzung nach Anspruch 2 zur Herstellung eines Medikaments zur Behandlung einer Störung des sexuellen Verlangens, einer Funktionsstörung der sexuellen Erregung, einer funktionellen Orgasmusstörung oder einer Störung mit sexuell bedingten Schmerzen.

8. Verwendung nach Anspruch 7, wobei der Patient weiblich ist.

9. Verwendung nach Anspruch 7, wobei der Patient männlich ist.

10. Verwendung nach Anspruch 7, wobei die Zusammensetzung oral, über die Wangenschleimhaut, örtlich, durch Injektion, durch Inhalationsspray oder transurethral verabreicht wird.

11. Verwendung nach Anspruch 10, wobei die Zusammensetzung oral als feste oder flüssige Dosierung verabreicht wird.

12. Kit, umfassend einen oder mehrere Behälter, die mit mindestens einer Verbindung nach Anspruch 1 gefüllt sind.

13. Kit nach Anspruch 12, weiter umfassend mindestens ein Mittel zur Verbesserung der Penetrationsfähigkeit.

14. Verbindung, ausgewählt aus 4-Aza-4-(2-methyl-2-sulfanylpropyl)tricyclo-(5.2.1.0<2,6>)dec-8-en-3,5-dion oder einem pharmazeutisch verträglichen Salz davon; 4-{1-Methyl-1-((2,4,6-trimethoxyphenyl)methylthio)ethyl}-1,3-oxazolidin-2-on oder einem pharmazeutisch verträglichen Salz davon; und 2-Amino-3-methyl-3-((2,4,6-trimethoxyphenyl)methylthio)butan-1-ol oder einem pharmazeutisch verträglichen Salz davon.

15. 4- Aza- 4-(2- methyl- 2-(nitrosothio) propyl) tricyclo (5.2.1.0<2,6>)dec-8-en-3,5-dion oder ein pharmazeutisch verträgliches Salz davon.

16. 4-(1-Methyl-1-(nitrosothio)ethyl)1,3-oxazolidin-2-on oder ein pharmazeutisch verträgliches Salz davon.

Revendications

1. Composé choisi parmi la 4-aza-4-(2-méthyl-2-(nitrosothio)-propyl)tricyclo(5.2.1.0<2,6>)déc-8-ène-3,5-dione ou un sel pharmaceutiquement acceptable de celle-ci ; et la 4-(1-méthyl-1-(nitrosothio)éthyl)-1,3-oxazolidin-2-one ou un sel pharmaceutiquement acceptable de celle-ci.

2. Composition comprenant le composé selon la revendication 1 et un support pharmaceutiquement acceptable.

3. Composition selon la revendication 2, comprenant en outre au moins un améliorateur de pénétration.

4. Composition selon la revendication 3, dans laquelle l'améliorateur de pénétration est le diméthylsulfoxyde, le diméthylformamide, le N,N-diméthylacétamide, le décylméthylsulfoxyde, le monolaurate de po-

lyéthylène glycol, le polyéthylène glycol, le monolaurate de glycérol, la lécithine, une azacycloheptan-2-one substituée en 1, un alcanol inférieur, un 1,3-dioxane substitué par un groupe hydrocarbyle en C_6-C_{20}, un 1,3-dioxolane substitué par un groupe hydrocarbyle en C_6-C_{20} ou un acétal substitué par un groupe hydrocarbyle en C_6-C_{20}, un alconate, un glycéride, un tensioactif, ou un mélange de ceux-ci.

5. Composition selon la revendication 4, dans laquelle le glycéride est un monoglycéride, un diglycéride, un triglycéride, un glycéride polyglycolisé ou un mélange de ceux-ci.

6. Composition selon la revendication 5, dans laquelle le glycéride est un mélange de triglycérides capryliques et de triglycérides capriques, un décanoyltriglycéride, un octanoyltriglycéride, un triglycéride en C_8-C_{12}, un glycéride polyglycolisé saturé, un complexe de caprylate/caprate de glycéryle et de caprylate/caprate de PEG-8 (polyéthylène glycol), un glycéride polyglycolisé insaturé, un complexe d'huile de noyau d'abricot et de PEG-6, un complexe d'huile d'amande et de PEG-6, un complexe d'huile d'arachide et de PEG-6, un complexe d'huile d'olive et de PEG-6, un complexe d'huile de maïs et de PEG-6, un glycéride éthoxylé, un complexe de caprylate/caprate de glycéryle et de PEG-4, ou un mélange de ceux-ci.

7. Utilisation d'une composition selon la revendication 2, pour la fabrication d'un médicament destiné à traiter un trouble du désir sexuel, un dysfonctionnement de l'éveil sexuel, un dysfonctionnement orgasmique ou une douleur sexuelle.

8. Utilisation selon la revendication 7, dans laquelle le patient est une femme.

9. Utilisation selon la revendication 7, dans laquelle le patient est un homme.

10. Utilisation selon la revendication 7, dans laquelle la composition est administrée par voie orale, buccale, topique, par injection, par pulvérisation par inhalation ou par application transuréthrale.

11. Utilisation selon la revendication 10, dans laquelle la composition est administrée par voie orale sous la forme d'une dose solide ou liquide.

12. Kit comprenant un ou plusieurs récipients rempli(s) avec au moins un composé selon la revendication 1.

13. Kit selon la revendication 12, comprenant en outre au moins un améliorateur de pénétration.

14. Composé choisi parmi la 4-aza-4-(2-méthyl-2-sulfanylpropyl)tricyclo(5.2.1.0<2,6>)déc-8-ène-3,5-dione ou un sel pharmaceutiquement acceptable de celle-ci ; la 4-{1-méthyl-1-((2,4,6-triméthoxyphényl)méthylthio)éthyl}-1,3-oxazolidin-2-one ou un sel pharmaceutiquement acceptable de celle-ci ; et le 2-amino-3-méthyl-3-((2,4,6-triméthoxyphényl)méthylthio)butan-1-ol ou un sel pharmaceutiquement acceptable de celui-ci.

15. 4- aza- 4-(2- méthyl- 2-(nitrosothio) propyl) tricyclo (5.2.1.0<2,6>)déc-8-ène-3,5-dione ou un sel pharmaceutiquement acceptable de celle-ci.

16. 4-(1-méthyl-1-(nitrosothio) éthyl)-1,3-oxazolidin-2-one ou un sel pharmaceutiquement acceptable de celle-ci.

Figure 1

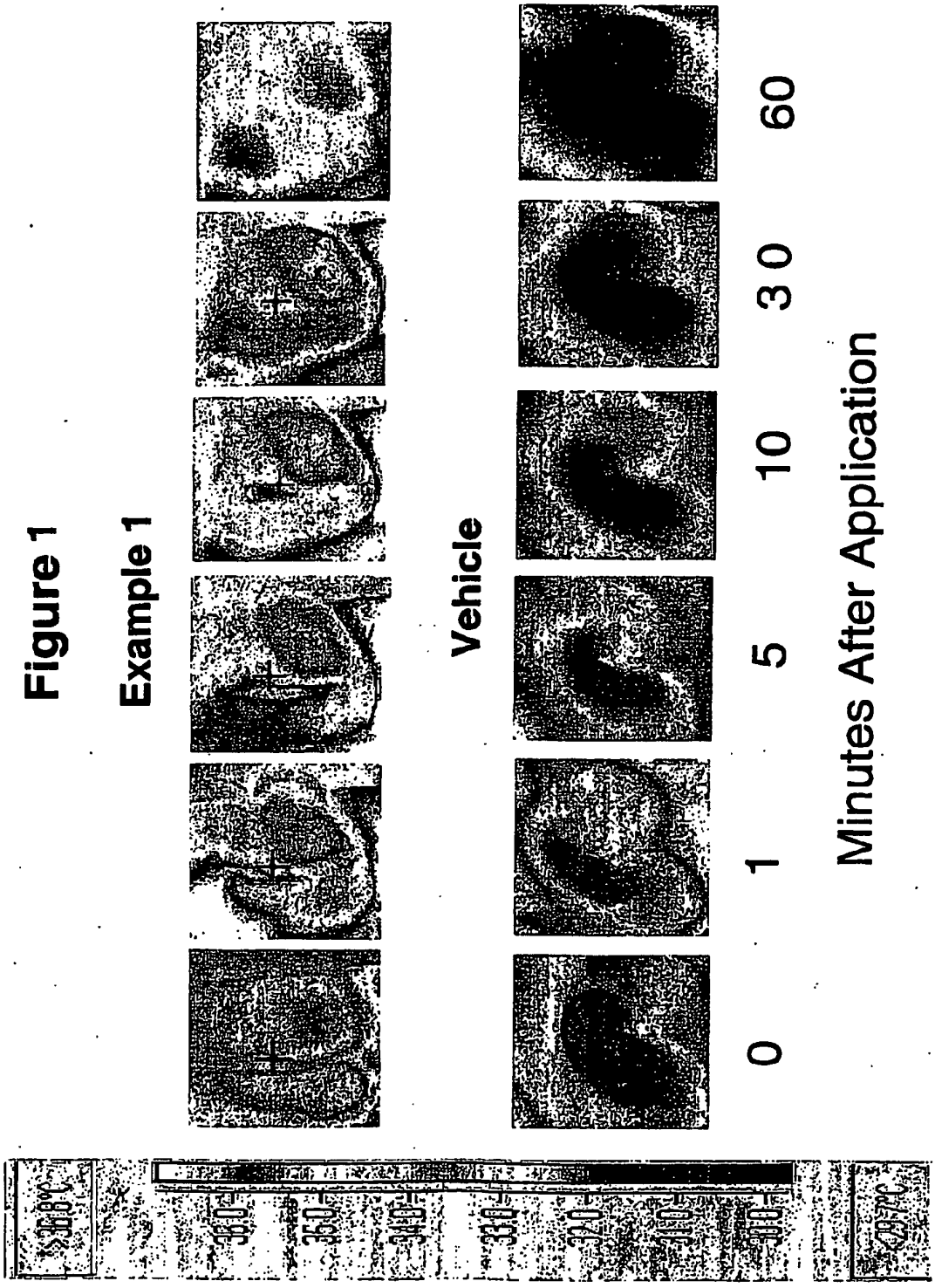
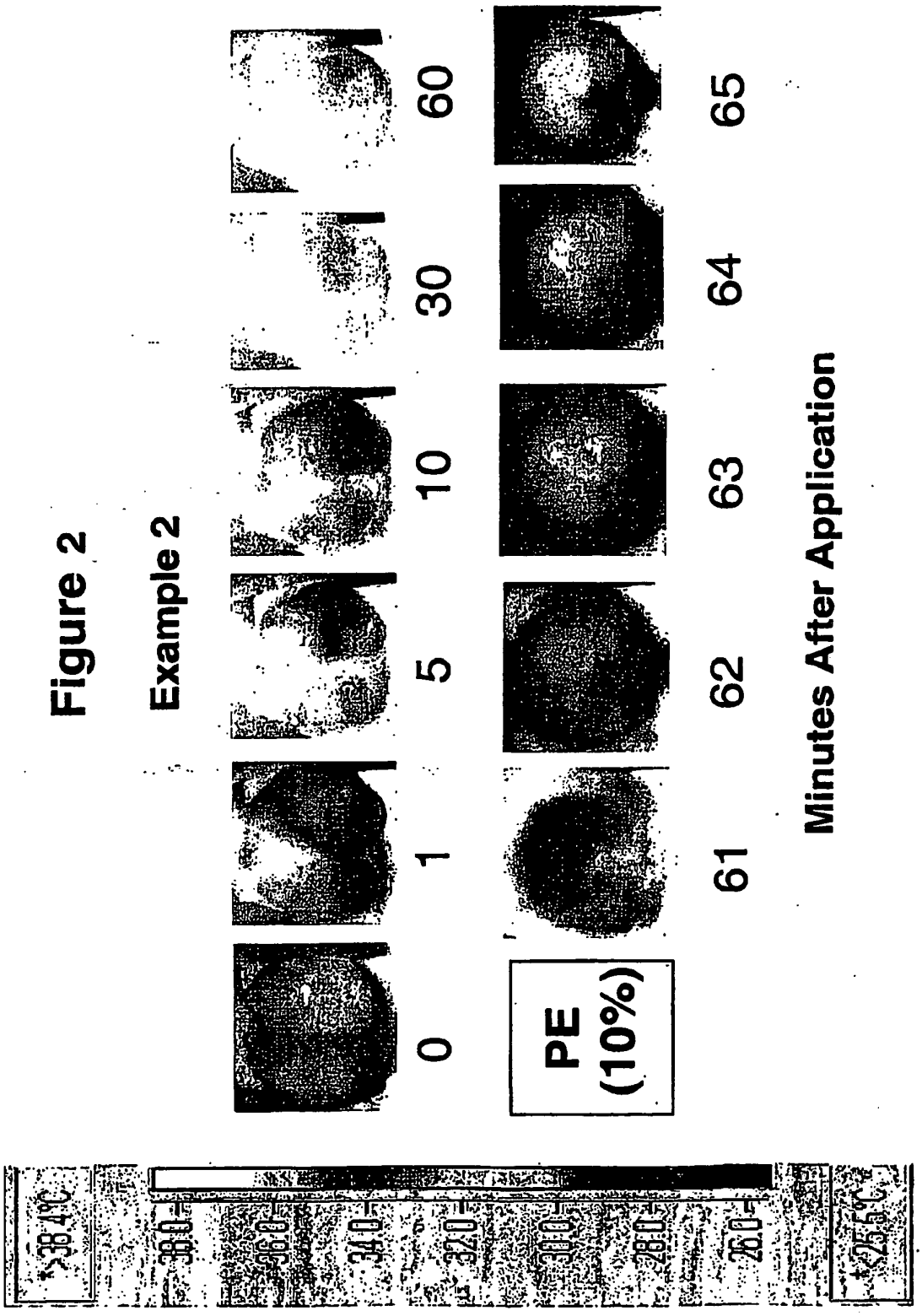


Figure 2


Example 2
PE (10%)
0
1
5
10
30
60
61
62
63
64
65
Minutes After Application
38.4°C
38.0
36.0
34.0
32.0
30.0
28.0
26.0
25.6°C

REFERENCES CITED IN THE DESCRIPTION

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