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(57) Abstract

6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione and pharmaceutically acceptable salts thereof are neurologically active steroids.

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NEUROLOGICALLY ACTIVE AMINOSTEROIDS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The hydroxylated and reduced A-ring steroids of the present invention are useful for treating neurological disorders.

2. Description of the Related Art

International Publication No. WO87/01706 based on International Patent Application No. PCT/US86/01797 and US Patent US 5,175,281 disclose 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione (EXAMPLE 83) and the mesylate salt (EXAMPLE 109) for use as neurological agents.

US Patent 4,968,675 discloses a parenteral formulation of 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione.

The Journal of Pharmacology and Experimental Therapeutics, 269, 145-50 (1994), *International Journal of Clinical Pharmacology and Therapeutics*, 32, 223-230 (1994) and *Pharmaceutical Research*, 11(2) 341 (1994) disclose 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione.

The compounds of the present invention, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are metabolites of a neurologically active pharmaceutical, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, see US Patent 5,175,281 (EXAMPLES 83 and 109).

Cosolvents have become widely used as a means for solubilizing drugs for non-parenteral and parenteral (both IV and IM) administration. The effect is dependent primarily upon the polarity of the drug with respect to the solvent (water) and the cosolvent. The degree to which the solubility of a drug can be increased for a particular cosolvent is dependent upon the nonpolarity of the drug and the nonpolarity of the cosolvent. The most frequently used cosolvents are propylene glycol, ethanol, glycerine, and polyethylene glycol. The solubilization curves of a

number of pharmaceutically important solutes in cosolvent systems is known, Techniques of Solubilization of Drugs, edited by S. H. Yalkowsky, Marcel Dekker, INC 1981, more particularly see Solubilization of Drugs by Cosolvents, p 91-134.

US Patent 4,794,117 and International Publication No. WO85/04106 disclose that solubilization of hydrophobic pharmaceuticals, eg. steroids, may be accomplished by solution in polyethylene glycol and addition of aqueous solutions of controlled pH and buffering.

Buffers in parenteral formulations are known.

Journal of Pharmaceutical Science and Technology, 48, 86-91 (1994) discloses that for that particular drug lower acetate buffer concentration caused less irritation than higher acetate buffer concentration. It was further disclosed that citrate buffer concentration of 0.01 M caused less irritation than acetate buffer concentration at 0.005 M with the particular drug used.

SUMMARY OF INVENTION

Disclosed are compounds selected from the group consisting of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione in substantially pure form, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione in substantially pure form and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione in substantially pure form and pharmaceutically acceptable salts thereof.

Also disclosed is a pharmaceutical composition which comprises a compound selected from the group consisting of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione pharmaceutically acceptable salts thereof and pharmaceutically acceptable carriers.

Further disclosed is a compound selected from the group consisting of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-

3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione, pharmaceutically acceptable salts thereof to prepare a medicament to treat a warm blooded mammal for a neurological disorder.

DETAILED DESCRIPTION OF THE INVENTION

6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione is prepared as set forth in the EXAMPLES 1, 2, 4 and 6.

6β-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione is prepared as set forth in the EXAMPLES 1-3 and 5.

21-[4-[2,6-Bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione is prepared as set forth in the EXAMPLES 7 thru 11. 21-[4-[2,6-Bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione is prepared as set forth in the EXAMPLES 7 thru 9, 12 and 13.

It is preferred that 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione be in the form of a pharmaceutically acceptable salt. It is preferred that the pharmaceutically acceptable acid addition anion salt be prepared by reacting the free base of the 21-aminosteroids with an approximately stoichiometric amount of an acid such as hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, lactic, citric, salicylic, pamoic, cyclohexanesulfamic, methanesulfonic, naphthalenesulfonic, p-toluenesulfonic, CH_3-$(CH_2)_{n1}$-COOH where n_1 is 0 through 4, HOOC-$(CH_2)n_1$-COOH where n is as defined above, HOOC-CH=CH-COOH, ϕ-COOH. It is preferred that the salt be selected from the group consisting of hydrochloride, hydrobromide, maleate, methanesulfonate and sulfate.

The 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-

pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione should be administered as a pharmaceutical composition as is known to those skilled in the art. It is preferred that pharmaceutial formulation be a solution for injection. The solution can either be aqueous as set forth in US Patent 4,968,675 or a co-solvent formulation as described below.

The sterile aqueous cosolvent parenteral formulation of the present invention contains one or more of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione , or a pharmaceutically acceptable salt, citrate (buffer), a cosolvent and water. Operable pharmaceutically acceptable acid addition salts include the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, lactate, citrate, succinate, benzoate, salicylate, pamoate, cyclohexanesulfanate, methanesulfonate, naphthalenesulfonate, p-toluenesulfonate, maleate, fumarate and oxalate, preferred is the mesylate (monomethanesulfonate) salt. The amount of the active therapeutic agent necessary is from about 0.9 to about 90 mg/ml of the free base or "free base equivalents". If the salt form is used a molar equivalent amount is necessary as is known to those skilled in the art. The citrate is present for its buffering function. The buffer can be added as a buffering system (citric acid plus a salt of citric acid) or it can be generated in situ by adding either the acid or the salt of the acid and then adjusting the pH. Suitable citrate salts include sodium, potassium and ammonium and the equivalents there of. It is preferred to add the buffering system premade rather than generate it in situ. The operable amount of citrate is from about 0.002 to about 2.0 M. Operable cosolvents include for example the alcohols propylene glycol, polyethylene glycol, glycerol and ethanol as well as DMSO, DMAC, DMI and M-PYROL or their equivalents; it is preferred that the

cosolvent be an alcohol selected from the group consisting of propylene glycol, polyethylene glycol, glycerol and ethanol, more preferably that the cosolvent be propylene glycol. The amount of the cosolvent necessary is any amount up to about 80%, depending on which particular cosolvent is used. It is preferred that the cosolvent be present in an amount of from about 1 to about 80%, more preferably from about 20 to about 60%. When the amount of the 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione to be solubilized is 25 mg/ml, it is preferred that the propylene glycol be present in about 40%. Water is added in sufficient amounts to bring the mixture to volume. The sterile aqueous cosolvent parenteral formulation of the present invention is prepared as is known to those skilled in the art. More specifically and preferably the citrate buffers are dissolved in about 50 to about 70% of the available water. Next the cosolvent is added and mixed. Following addition of the cosolvent the one or more of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione is added, the pH adjusted and sufficient water added to volume. Optionally, the isotonicity can be adjusted to physiological levels, if that is desired the isotonicity adjusting agent is added when the citrate is added. Finally, the mixture is sterilized as is known to those skilled in the art.

The sterile aqueous cosolvent pharmaceutical composition for parenteral administration is in concentrated form and is meant to be diluted (to the desired concentration of the lazaroid prior to administration to the patient. It can be diluted with physiological (normal or 0.9%) saline or 5% dextrose in water or mixtures thereof, or any other vehicle used in parenteral administration except for lactated Ringers solution. The critical requirement is the pH, if it is too high or buffered too high (over about 5) the lazaroid will precipitate out. Alternatively, the sterile aqueous pharmaceutical composition for parenteral administration can be

administered in its concentrated form. This is most likely to be performed in emergency situations where there is insufficient time for dilution. The only problem with administering the concentrated formulation is vascular irritation and damage. However, some emergency situation might justify this use. If done, it is recommended not to use this vein for follow up administration.

The sterile aqueous cosolvent pharmaceutical composition for parenteral administration of the invention should be refrigerated, but not stored below - 5°.

6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in treating and/or preventing spinal injury mild and/or moderate to severe head injury, subarachnoid hemorrhage (SAH) and subsequent ischemic stroke, asthma and reduction of mucous formation/-secretion in the lung, muscular dystrophy, adriamycin cardiac toxicity, Parkinsonism, other degenerative neurological disorders, multiple sclerosis, organ damage during reperfusion after transplant, preservation of transplant organs by treatment of the donor, skin graft rejection, hemorrhagic, traumatic and septic shock, and conditions such as severe burns, ARDS, chemical oxidant-induced injury to the kidney (for example, inhibition of contrast dye nephropathy and inhibition of cyclosporine toxicity) nephrotic syndrome (immunological), systemic lupus erythematosus, allergic reactions, atherosclerosis, inflammation (dermatological antiinflammatory and antipsoriasis agents), emphysema, cancer (limit metastasis, limit tumor growth), (stress induced) ulcers, ulcerative colitis and Crohn's disease. The compounds are also useful for prophylactic treatment before surgical procedures such as hip and jaw surgery where 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione reduces edema. They are useful for preventing neurologic injury during surgical procedures and neurological procedures, for treatment of myocardial infarctions, for treatment after resuscitation to improve outcome, particularly

neurological outcome post resuscitation, drug allergic reactions and migraine headaches. The compounds have use in ophthalmology, e.g., in treatment of diabetic retinopathy, age-related macular degeneration, cataracts and glaucoma, light-induced retinal damage and in irrigation mixtures used in eye surgery, prevention of hyperoxic injury in adults and infants, reduction of facial edema after surgical procedures such as oral/facial surgery or trauma from accidents. 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione also can be co-administered with anti-cancer drugs such as adriamycin, taxol or vinblastine when the tumor or cell strain becomes resistant as 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are effective inhibitors of multiple drug resistance. 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are also useful in protection from radiation injury, particularly in brain and gut. In case of the gut, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione can be administered topically (e.g. by suppository) or by other more common routes. This is particularly helpful in preventing gut injury during prostate irradiation.

In humans, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-

piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in treating subarachnoid hemorrhage and subsequent cerebral vasospasm, global cerebral ischemia post resuscitation (CPR) to prevent post-ischemic brain damage, brain tumor (neuroprotective), Bells Palsy, other degenerative neurological disorders, hepatic necrosis (e.g. from viral hepatitis), some forms of radiation damage (for example during radiation treatment or from accidental exposure to radiation), myocardial damage after myocardial ischemia, pre-birth infant strangulation and infant hypoxia syndrome, such ophthalmic disorders as uveitis and optic neuritis and ischemic bowel syndrome.

In humans, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in preventing damage following cardiopulmonary resuscitation, neurological or cardiovascular surgery and from cardiac infarction, ocular damage after ophthalmic surgery (e.g. cataritic surgery).

It is preferred that 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in treating complications of surgery or trauma such as edema and neurologic injury and renal injury. Generally, these four compounds are used like the glucocorticoid pharmaceuticals for the treatment of the above human conditions as well as the animal conditions listed below. While these four compounds are useful in both humans and animals in treating many of the same conditions and preventing complications and damage from the same problems as the glucocorticoids, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-

dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in treating a number of conditions and preventing damage from conditions where the glucocorticoids are not useful. 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione have no glucocorticoid activity and therefore, unlike the glucocorticoids, they can be given daily for longer periods of time without the side effects associated with the glucocorticoids. This is a distinct advantage. They have no effect on blood glucose and this is also an advantage.

It is to be understood that 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione will be more useful to a different degree to treat some of these conditions than others.

The standard conditions for treatment are to give 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione orally or parenterally, e.g. IV (that is by injection, infusion or continuous drip) or IM, with a standard dose of about 5 to about 20 mg/kg/day IV for up to 20 days (with 10 days being sufficient for some conditions) or about 5 to about 30 mg/kg/day; one to four times daily by mouth. Females may be given higher doses than males since, on the average, they may metabolize 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-

dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione more rapidly than males. For females the standard dose is from about 7 to about 30 mg/kg/day IV or about 7 to about 50 mg/kg/day one to four times daily by mouth. For example, in treatment of SAH males may be give 10 mg/kg/day and women given 15 mg/kg/day. The dose can be administered as a single injection or, more typically, by divided doses (usually three or four times daily).

In treating SAH the patient should be treated with from about 6 mg/kg/day to about 20 mg/kg/day, preferably from about 10 to about 15 mg/kg/day.

In treating mild and moderate to severe head injury the patient should be treated with from about 10 mg/kg/day to about 20 mg/kg/day, preferably from about 10 to about 15 mg/kg/day.

In treating ischemic (thromboembolic) stroke the patient should be treated with an initial dose of from about 10 to about 25 mg/kg on day one, preferably from about 12.5 mg (males) and 15 mg (females) to about 20 mg/kg, to be followed by about 10 mg (males) and about 12.5 mg/kg (females) to about 20 mg/kg for about 3 days.

In treating spinal cord injury the patient is treated with 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione of about 5 to about 20 mg/kg/day for one to a few days. It is preferable to treat those with spinal cord injury with about 10 to about 20 mg/kg/day for one day. When treating patients with spinal cord injury it is also preferable to give them a one time large dose of a steroid such as methylprednisolone sodium succinate prior to the administration of the 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-

pregna-1,9(11)-diene-3,20-dione.

For treating damage following cardiopulmonary resuscitation, cardiac infarction, organ damage during reperfusion after transplant, hemorrhagic, traumatic and septic shock, severe burns, ARDS, and nephrotic syndrome and preventing skin graft rejection, the standard conditions are used. Typical treatment may involve an initial loading dose, e.g. an IV dose of 0.05 mg to 4 mg/kg followed by maintenance dosing usually given four times a day by IV bolus infusion for one to 10 days depending on the particular condition of the patient and the particular compound used. This may be supplemented with IM or oral dosing for days, weeks or months. In treating inflammatory lung maladies such as asthma, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are administered orally, IV and by inhalation in the standard dose. In treating excess mucous secretions, the oral dose is from about 5 to about 30 mg/kg/day. The frequency of administration is one through 4 times daily. The oral administration of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione to treat excess mucous secretions may go on for months or even years. The susceptible individuals can be pre-treated a few hours before an expected problem. The IV dose is about 5 to about 20 mg/kg/day. The aerosol formulation contains about 0.01 to about 1.0% of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are administered or used about four times daily as needed. In treating muscular dystrophy, Parkinsonism, and other degenerative neurological disorders (amyotrophic lateral sclerosis; multiple sclerosis)

6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are administered orally using a dose of about 5 to about 30 mg/kg/day, administered or used one to four times a day. The treatment may go on for years.

In treating adriamycin-induced cardiac toxicity, these four compounds are administered orally or IV using a dose of about 1.0 to about 50 mg/kg/day, preferably about 5 to about 20 mg/kg/day. 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are preferably given concomitantly with IV adriamycin or the individual is pre-treated with 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione.

For prophylaxis prior to and preventing damage after neurological or cardiovascular surgery, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are used according to the standard conditions. The patient can be pretreated with a single IV or IM dose just prior to and after surgery or orally before and after surgery.

In treating drug allergic reactions, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-

hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are given in a dose of about 5 to 20 mg/kg/day, administered one to four times daily IV and about 5 to about 30 mg/kg/day orally. Typical treatment would be an initial IV loading dose followed by oral dosing for a few days or more.

In treating atherosclerosis and emphysema, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are given orally in a dose of about 5 to about 30 mg/kg/day, one to four times daily for months or years. These four compounds are useful in treatment of premature infants who may be maintained in a high oxygen environment. 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione improve morbidity and mortality in these cases which are paretically susceptible to intracranial bleeding and bronchopulmonary dysplasia. In this situation the standard treatment is given either IV or orally.

In treating dermatological inflammatory conditions including psoriasis, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are given orally in a dose of about 5 to about 30 mg/kg/day, once or the amount can be given two to four times daily in divided doses or applied topically as a cream, ointment or lotion or equivalent dosage form in a concentration of about 0.05 to about 5% as long as needed. In

treating these conditions 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione can be used with steroidal agents.

6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in the prevention and treatment of stress ulcers and of gastric intolerance caused by drugs such as nonsteroidal anti-inflammatory compounds (NOSAC). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, sepsis, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress ulcers also include lesions that can lead to upper gastrointestinal bleeding; such bleeding is likely to be prevented by these compounds. NOSAC includes drugs such as ibuprofen, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal intolerance characterized by pain and lesions that may lead to bleeding. 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione will be administered preferentially by the oral route either as tablets, capsules or liquids, in doses ranging from about 25 to about 500 mg, two to four times a day. The treatment would be either preventive, i.e., starting before ulcers have formed in patients at risk of developing such lesions, or therapeutic, i.e., once the ulcers have formed. In patients whose clinical condition precludes swallowing the oral dosage forms, these four compounds are given either through a nasogastric tube, or parenterally, i.e., IV or IM. The parenteral doses would range from about 5 to about 100 mg and be

administered one to four times a day or by IV.

In dogs, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in treating trauma, intervertebral diseases (slipped disk), traumatic shock, flea bite and other allergies.

In horses, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione are useful in treating endotoxic or septic shock which follows colic, pretreatment before surgery for colic and treatment of Founder (laminitis). 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione can reduce muscle damage that is a common occurrence during surgical procedures that require that the horse be prone for long periods during surgery.

In cattle, these four compounds are useful in treating acute coliform mastitis, bovine mastitis, acute allergic reaction to feed lot vaccination and shipping fever.

In pigs, these four compounds are useful in treating porcine stress syndrome and thermal stress syndrome.

The term treatment or treating as used in this patent is used broadly and includes both treatment of an existing condition as well as preventing the same condition from occurring where such is possible as is well known to those skilled in the art. For example, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-

3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione can be used to treat existing asthma conditions and to prevent future ones from occurring. For example, 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione treat spinal trauma and prevent rejection of skin grafts.

6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione can be used with each other and/or can be used with other pharmaceutical agents in treatment of the conditions listed above as is known to those skilled in the art.

In many instances it may be preferable to administer an inhibitor of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione metabolism such as ketoconazole or TAO (triacetyloleandomycin) prior to or concurrently with 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione administration to raise the blood level of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-

16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione and/or certain of its metabolites. Because females may metabolize 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione more rapidly than males, administration of an inhibitor of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione metabolism can raise blood levels in females to that of males. For example, ketoconazole should be administered in an amount of about 50 to about 300 mg/day, preferably about 200 mg/day about 1 to about 2 hr for acute uses and about 1 to about 3 hr for repeat dose situations.

Since agents such as phenobarbital and phenytoin decrease the blood levels of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione, it is preferable to increase the dose of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione given to individuals who either were taking or will be administered any agent which will decrease the blood level of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-

methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione.

The exact dosage and frequency of administration of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione depends on the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione (or biologically active metabolite thereof) in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support, eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from tetramethylsilane.

TMS refers to trimethylsilyl.

MS refers to mass spectrometry expressed as m/e or mass/charge unit. $[M + H]^+$ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 3,20,21-Trihydroxy-16α-methylpregna-1,3,5,9(11),17(20)-pentaene 21-acetate 3,20-dibenzoate

Benzoyl chloride (2.5 ml, 22 mmol) is added to a mixture of 21-hydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione 21 acetate (1.02 g, 2.67 mmol) and pyridine (9.0 ml). The mixture is heated at 75° for 16 hr and is allowed to cool to 20-25°. The residue is diluted with ethyl acetate (200 ml) which is washed with hydrochloric acid (10%, 3 x 60 ml) and saline (100 ml). The organic phase is dried over magnesium sulfate, filtered and concentrated. The concentrate is triturated with hexane/ether (20/1) to remove excess benzoyl chloride and the residue purified by flash chromatography (silica gel; eluting with hexane/ethyl acetate (3/1)) to give 367 mg (23%) of the title compound, NMR (300 MHz, $CDCl_3$) 8.05-8.2, 7.55-7.7, 7.4-7.55, 6.20, 5.85-5.95, 5.6-5.7, 5.35-5.45, 4.63, 2.19, 1.33, 1.00 and 0.70 δ.

EXAMPLE 2 6α,20,21-Trihydroxy-16α-methylpregna-1,4,9(11),17(20)-tetraen-

3-one 21-acetate 20-benzoate and 6β,20,21-Trihydroxy-16α-methylpregna-1,4,9(11),17(20)-tetraen-3-one 21-acetate 20-benzoate

A mixture of potassium peroxymonosulfate (1.70 g, 2.77 mmol) and water (10 ml, neutralized with sodium bicarbonate) is added over 30 min to a mixture of the 3,20,21-trihydroxy-16α-methylpregna-1,3,5,9(11),17(20)-pentaene 21-acetate 3,20-dibenzoate (EXAMPLE 1, 900 mg, 1.52 mmol) and THF (25 ml). The mixture is stirred for 16 hr at 20-25° and is then diluted with ethyl acetate (125 ml). The organic phase is washed with water (40 ml), sodium thiosulfate (10%, 2 x 40 ml - no color to starch-iodine paper), and saline (40 ml). The organic phase is dried over magnesium sulfate, filtered, and concentrated. The concentrate is purified by flash chromatography (silica gel; eluting with ethyl acetate/hexane (1/1)) to give the 6-β hydroxy isomer, NMR (300 MHz, $CDCl_3$) 8.13, 7.63, 7.49, 7.18, 6.28, 6.18, 5.5-5.6, 4.55-4.65, 4.60, 2.18, 1.63, 0.99 and 0.74 δ.

Further elution provides the 6-α hydroxy isomer, NMR (300 MHz, $CDCl_3$) 8.13, 7.64, 7.49, 7.15, 6.45-6.5, 6.33, 5.5-5.6, 4.65-4.75, 4.60, 2.18, 1.39, 0.98 and 0.71.

EXAMPLE 3 6β,21-Dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione

A mixture of 6β,20,21-trihydroxy-16α-methylpregna-1,4,9(11),17(20)-tetraen-3-one 21-acetate 20-benzoate (EXAMPLE 2, 220 mg, 0.438 mmol), methanol (12 ml) and saturated sodium bicarbonate (2.0 ml) is stirred for 48 hr at 20-25°. The methanol is removed under reduced pressure and the aqueous layer saturated with sodium chloride. The residue is extracted with methylene chloride (6 x 15 ml), dried (over magnesium sulfate), filtered and concentrated to give the title compound, mp 210-212°; IR (mineral oil) 3442, 1702, 1665, 1625 and 1057 cm^{-1}; NMR (300 MHz, $CDCl_3$) 7.19, 6.27, 6.15-6.2, 5.5-5.6, 4.55-4.65, 4.15-4.25, 3.25-3.35, 2.6-2.9, 1.64, 1.00 and 0.72 δ; MS (EI, m/e) 356, 325, 279, 253 and 197.

EXAMPLE 4 6α,21-Dihydroxy-16α-methyl-1,4,9(11)-triene-3,20-dione

Following the general procedure of EXAMPLE 3 and making non-critical variations but starting with 6α,20,21-trihydroxy-16α-methylpregna-1,4,9(11),17(20)-tetraen-3-one 20-benzoate (EXAMPLE 2, the title compound is obtained, IR (mineral oil) 3407, 1714, 1662,1619,1604 and 1057 cm^{-1}; NMR (300 MHz, $CDCl_3$) 7.16, 6.47, 6.31, 5.45-5.6, 4.69, 4.1-4.3, 3.2-3.4, 2.7-2.9, 1.39, 1.00 and 0.69 δ; MS (EI, m/z) 357, 356, 339 and 121.

EXAMPLE 5 6β-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione

Methanesulfonyl chloride (9.1 µl, 0.12 mmol) is added to a mixture of the alcohol 6β,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione (EXAMPLE 3, 40.0 mg, 0.112 mmol), methylene chloride (2.0 ml) and diisopropylethylamine (21 µl, 0.12 mmol) at 0°. The mixture is stirred at 0° for 2 hr and at 20-25° for 1 hr at which time starting material is still present by TLC analysis. The reaction mixture is recooled to 0° and is pulsed with additional methanesulfonyl chloride (9.1 µl) and diisopropylethylamine (21 µl). After stirring for an additional hour at 0°, the reaction is complete by TLC analysis. Basic workup (methylene chloride, dilute sodium bicarbonate and magnesium sulfate) provide the mesylate which is carried on crude.

A mixture of the mesylate, 4-(1-piperazinyl)-2,6-di-1-pyrrolidinylpyrimidine (37.0 mg, 0.122 mmol), potassium carbonate (17 mg, 0.12 mmol) and acetonitrile (2.0 ml) is stirred at 20-25° for 16 hr and at 50° for 8 hr. After being allowed to cool to 20-25°, aqueous workup (methylene chloride/magnesium sulfate) and purification by flash chromatography (eluting with ethyl acetate) gives the title compound, NMR (300 MHz, $CDCl_3$) 7.18, 6.27, 6.15, 5.5-5.6, 4.86, 4.55-4.65, 3.18, 1.63, 0.97 and 0.71; MS (EI, m/e) 640, 315 and 246.

EXAMPLE 6 6α-Hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione

Following the general procedure of EXAMPLE 5 and making non-critical variations, but starting with 6α,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione (EXAMPLE 4), the title compound is obtained.

EXAMPLE 7 21-Hydroxy-16α-methylpregna-4,9(11)-diene-3,20-dione 21-acetate

Aqueous hydrochloric acid (1N, 65 ml) is added to a stirred mixture of 21-hydroxy-20-trimethylsilyloxy-16α-methylpregna-4,9(11),17(20)-trien-3-one 21-acetate (24.4 g, 53.5 mmol) in acetone (400 ml). TLC analysis indicates completion of the reaction after 15 minutes. Removal of the solvent gives a solid. This solid is dissolved in methylene chloride and washed with dilute sodium bicarbonate, water, and saline. The phases are separated and the organic phase is dried over sodium sulfate, filtered and the solvent removed by evaporation to give a concentrate. The concentrate is chromatographed using a flash system (silica gel, 750 g of 230-400 mesh; eluting with methylene chloride/acetone (97/3-95/5)). Collection of the appropriate fractions followed by solvent evaporation and drying under high vacuum gives the title compound, mp 142-145°; NMR ($CDCl_3$, TMS) 5.76, 5.5, 4.73, 4.47,

2.78, 2.18, 1.33, 0.98, 0.68 δ.

EXAMPLE 8 21-Hydroxy-16α-methyl-5α-pregn-9(11)-ene-3,20-dione 21-acetate and 21-hydroxy-16α-methyl-5β-pregn-9(11)-ene-3,20-dione 21-acetate

21-Hydroxy-16α-methylpregna-4,9(11)-diene-3,20-dione 21-acetate (EXAMPLE 7, 19.5 g, 0.057 mol) is dissolved in ethyl acetate (300 ml) and poured into a 2 liter Parr flask. To this mixture palladium on carbon (5%, 0.77 g) is added under an argon atmosphere. The reaction is placed under 40 psi of hydrogen gas and shaken for 18 hr. The suspension is filtered through Celite followed by washing of the filter cake several times with ethyl acetate. Solvent evaporation and drying under high vacuum gives the title compounds, TLC (silica gel GF, in methylene chloride/acetone (95/5) gives R_f = 0.46.

EXAMPLE 9 21-Hydroxy-16α-methyl-5α-pregn-9(11)-ene-3,20-dione and 21-hydroxy-16α-methyl-5β-pregn-9(11)-ene-3,20-dione

A stirred suspension of 21-hydroxy-16α-methylpregn-9(11)-ene-3,20-dione 21-acetate (EXAMPLE 8, 14.1 g, 0.0367 mol) in methanol (375 ml) is heated to reflux to aid in dissolving suspended solids. The mixture is cooled to 20-25° and diluted with methylene chloride (75 ml). To this mixture is added aqueous potassium carbonate (10%, 30 ml). After 40 minutes glacial acetic acid (2.5 ml) is added followed by solvent evaporation. The remaining residue is partitioned between ethyl acetate/aqueous sodium bicarbonate. The organic phase is separated and washed with water and saline, dried over sodium sulfate, filtered, and concentrated. Two 6.1 g portions of the above concentrate are chromatographed separately using a flash system (silica gel, 230-400 mesh, 840 g; eluting with hexane/ethyl acetate/methylene chloride (3/2/1). A mixture of the title compounds are isolated and chromatographed an additional time using identical conditions to give the title compounds, 5α - mp 165-173°; NMR ($CDCl_3$, TMS) 5.35, 4.19, 3.30, 1.14, 0.98 and 0.62 δ and 5β - mp 127-130°; NMR ($CDCl_3$, TMS) 5.54, 4.20, 3.30, 1.14, 0.99 and 0.62 δ.

EXAMPLE 10 21-Hydroxy-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione

Palladium (II) chloride (1.4 g, 7.9 mmol) is treated with concentrated hydrochloric acid (1.9 ml) followed by evaporation of any volatiles under high vacuum and a nitrogen stream. The remaining residue is dissolved in tert-butanol (35 ml) and treated with 21-hydroxy-16α-methyl-5α-pregn-9(11)-ene-3,20-dione (EXAMPLE 9, 1.5 g, 4.35 mmol). The reaction mixture is heated to a gentle reflux for 2.5 hr. TLC analysis indicates incomplete consumption of starting material, but

also indicated formation of unwanted products which required that heating be discontinued. The above reaction mixture is cooled to 20-25° and treated with water. The reaction contents are poured into water/methylene chloride, followed by separation of the layers. The aqueous phase is extracted two additional times with methylene chloride. The combined organic phases are washed with water and saline, dried over sodium sulfate, filtered, and concentrated. The concentrate is chromatographed using a flash system (silica gel, 230-400 mesh, 160 g; eluting with methylene chloride/acetone (98/2) to give the title compound, mp 136-141°; NMR ($CDCl_3$, TMS) 7.4, 5.80, 5.65, 4.16, 3.76, 1.17, 0.94 and 0.61 δ; MS (EI) calc'd for $C_{22}H_{30}O_3$ (M)+ = 342, found = 342.

EXAMPLE 11 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione

A stirred solution of 21-Hydroxy-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione (EXAMPLE 10, 0.231 g, 0.674 mmol) in methylene chloride (10 ml) is cooled in an ice bath and treated with triethylamine (0.15 ml, 1.1 mmol) and methanesulfonyl chloride (75 µl, 0.97 mmol). The reaction is kept under a nitrogen atmosphere. After 30 minutes the reaction mixture is poured into 2% aqueous sodium bicarbonate/methylene chloride and the layers separated. The aqueous phase is extracted twice with methylene chloride. The combined organic phases are washed with saline and dried over sodium sulfate, filtered, and concentrated.

A stirred suspension of [2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]piperazine (US Patent 5,175,281, PREPARATION A-22, 0.208 g, 0.688 mmol), potassium carbonate (0.142 g, 1.03 mmol), and sodium iodide (23.8 mg, 0.159 mmol) in acetonitrile (20 ml), is heated to reflux under a nitrogen atmosphere. The product from the proceeding paragraph is taken up in acetonitrile (5 ml) and added to the refluxing suspension over a period of 10 minutes. After 2 hr the reaction is cooled to 20-25° and poured into a separatory funnel containing water/ethyl acetate. The layers are separated followed by extraction of the aqueous layer with ethyl acetate. The combined organic phases are washed with aqueous sodium bicarbonate and dried over sodium sulfate, filtered, and concentrated, The concentrate is chromatographed (silica gel, 70-230 mesh, 50 g; eluting with methylene chloride/acetone (85/15-8/2)), to give the title compound, mp 190-200°; NMR (d_6-acetone; TMS) 7.36, 5.80, 5.62, 4.98, 3.54, 3.45, 3.37, 3.26, 3.02, 1.17, 0.93 and 0.59 δ; MS (EI) calc'd for $C_{38}H_{54}N_6O_2$ (M)+ = 626.4308, found = 626.4293.

EXAMPLE 12 21-Hydroxy-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione

Following the general procedure of EXAMPLE 10 and making non-critical variations but starting with 21-hydroxy-16α-methyl-5β-pregn-9(11)-ene-3,20-dione (EXAMPLE 9), the title compound is obtained.

EXAMPLE 13 21-[4-[2,6-Bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione

Following the general procedure of EXAMPLE 11 and making non-critical variations but starting with 21-hydroxy-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione (EXAMPLE 12), the title compound is obtained, NMR ($CDCl_3$, TMS) 6.85, 5.96, 5.31, 4.84, 3.58, 3.51, 3.41, 3.15, 2.75, 1.32, 0.95 and 0.63 δ; MS (EI) Calc'd for $C_{38}H_{54}N_6O_2$ (M^+) = 626.4308, found = 626.4316.

EXAMPLE 14 Preferred Cosolvent Formulation

6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione mesylate	2.5 kg
citric acid, anhydrous	4.42 kg
sodium citrate, hydrous	588.0 g
propylene glycol	40.0 l
pH adjust with acid/base to 2.9	
water for injection, qsad	100.0 l

The citric acid and sodium citrate are dissolved in about 25 l of water for injection. The propylene glycol is added to the citrate mixture and mix thoroughly. The pH is adjusted to about 2.9. aaa mesylate is added and dissolved. The pH is checked and adjusted if needed. Lastly qs ad with water for injection. The final mixture is then sterilized.

EXAMPLE 15 High Dose And Low Buffer Ratio

6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione mesylate	10.0 kg
citric acid, anhydrous	10.8 kg
sodium citrate, hydrous	1.18 kg
propylene glycol	60.0 l
pH adjust with acid/base to 2.9	
water for injection, qsad	100.0 l

Following the general procedure of EXAMPLE 1 and making non-critical variations but using the ingredients above, the parenteral pharmaceutical composition is prepared.

EXAMPLE 16 High Buffer Ratio, Alternate Cosolvent And Nearly

Physiological Isosmotic

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione mesylate	1.0 kg
citric acid, anhydrous	3.46 kg
sodium citrate, hydrous	588.0 g
sodium chloride	300.0 g
propylene glycol	10.0 l
pH adjust with acid/base to 2.9	
water for injection, qsad	100.0 l

Following the general procedure of EXAMPLE 1 and making non-critical variations but using the ingredients above, the parenteral pharmaceutical composition is prepared.

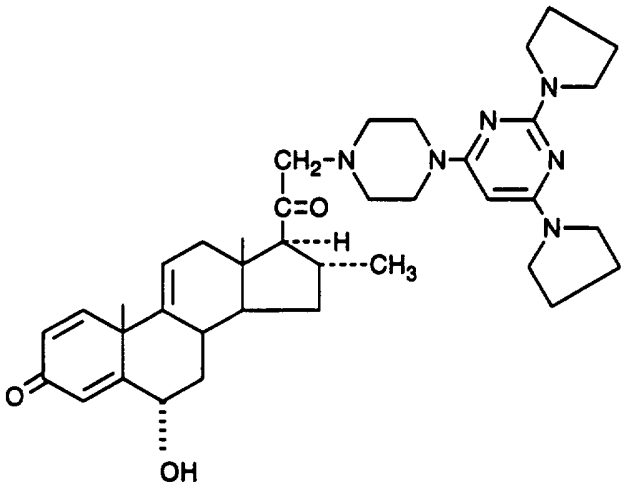
EXAMPLE 17 Low Dose, Low Propylene Glycol Concentration, In situ Buffer And Nearly Physiological Isosmotic

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione mesylate	100.0 g
citric acid, anhydrous	115.3 g
sodium chloride	850.0 g
propylene glycol	1.0 l
pH adjust with acid/base to 2.9	
water for injection, qsad	100.0 l

Following the general procedure of EXAMPLE 1 and making non-critical variations but using the ingredients above, the parenteral pharmaceutical composition is prepared.

CHART A

6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione



6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione

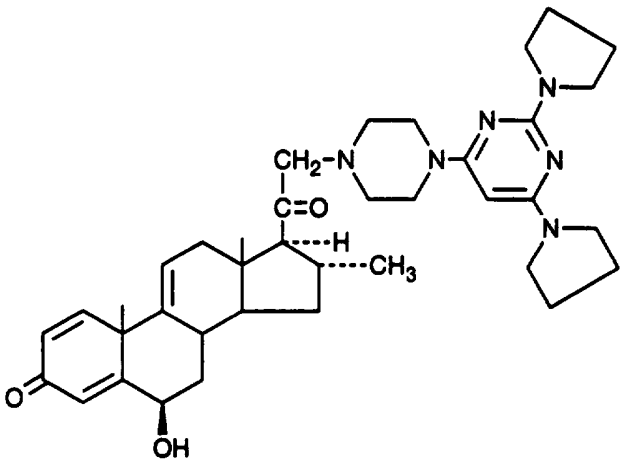
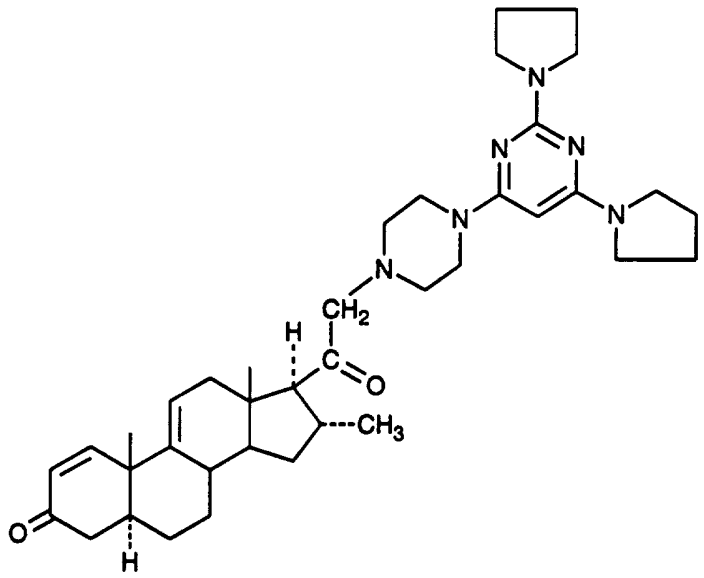
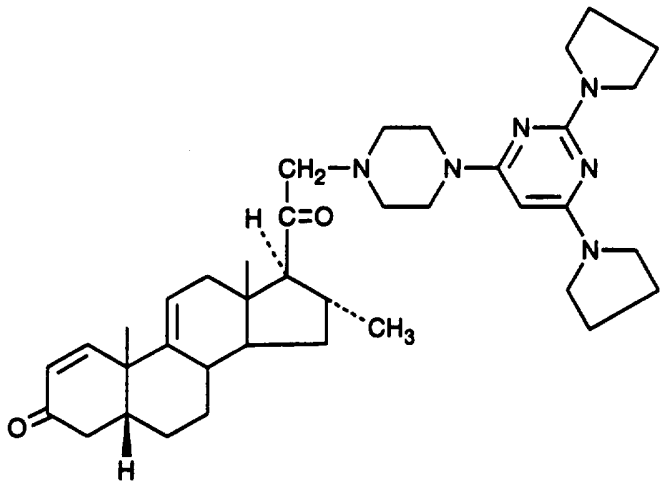


CHART B

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione



21-[4-[2,6-Bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione



CLAIMS

1. A compound selected from the group consisting of

6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione in substantially pure form,

6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione in substantially pure form and

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione in substantially pure form and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 where the pharmaceutically acceptable salt is a salt of an acid selected from the group consisting of hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, lactic, citric, salicylic, pamoic, cyclohexanesulfamic, methanesulfonic, naphthalenesulfonic, p-toluenesulfonic, CH_3-$(CH_2)_{n1}$-COOH where n_1 is 0 through 4, HOOC-$(CH_2)n_1$-COOH where n_1 is as defined above, HOOC-CH=CH-COOH and ϕ-COOH acids.

3. A compound according to claim 1 where the compound is 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione.

4. A compound according to claim 1 where the compound is 6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione.

5. A compound according to claim 1 where the compound is 21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione.

6. A pharmaceutical composition which comprises a compound selected from the group consisting of 6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione,

6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione,

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-

pregna-1,9(11)-diene-3,20-dione and

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione pharmaceutically acceptable salts thereof and pharmaceutically acceptable carriers.

7. A pharmaceutical composition according to claim 6 where the pharmaceutically acceptable salt is a salt of an acid selected from the group consisting of hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, lactic, citric, salicylic, pamoic, cyclohexanesulfamic, methanesulfonic, naphthalenesulfonic, p-toluenesulfonic, CH_3-$(CH_2)_{n1}$-COOH where n_1 is 0 through 4, HOOC-$(CH_2)n_1$-COOH where n_1 is as defined above, HOOC-CH=CH-COOH and ϕ-COOH acids.

8. A pharmaceutical composition according to claim 6 where the pharmaceutical composition is an aquesous solution for parenteral use.

9. A pharmaceutical composition according to claim 6 where the pharmaceutical composition is a cosolvent solution for parenteral use.

10. Use of a compound selected from the group consisting of

6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione,

6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione,

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione, pharmaceutically acceptable salts thereof to prepare a medicament to treat a warm blooded mammal for a neurological disorder.

11. Use of a medicament according to claim 10 where the useful warm blooded mammal is a human.

12. Use of a medicament according to claim 10 where the neurological trauma is selected from the group consisting of subarrachnoid hemmorhage (SAH), head injury, spinal cord injury/trauma, ischemic stroke, asthma, muscular dystrophy,

Parkinsonism, multiple sclerosis, traumatic shock, neurological outcome post resuscitation and migraine headaches.

13. Use of a medicament according to claim 12 the neurological trauma is selected from the group consisting of subarrachnoid hemmorhage, head injury, spinal cord injury/trauma and ischemic stroke.

14. Use of a medicament according to claim 10 where the effective amount of the compound selected from the group conisting of

6α-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione,

6β-hydroxy-21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione,

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5α-pregna-1,9(11)-diene-3,20-dione and

21-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methyl-5β-pregna-1,9(11)-diene-3,20-dione, pharmaceutically acceptable salts thereof is from about 5 to about 200 mg/kg/day orally and is from about 5 to about 30 mg/kg/day IV.

15. Use of a medicament according to claim 10 where the pharmaceutically acceptable salt is a salt of an acid selected from the group consisting of hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, lactic, citric, salicylic, pamoic, cyclohexanesulfamic, methanesulfonic, naphthalenesulfonic, p-toluenesulfonic, CH_3-$(CH_2)_{n1}$-COOH where n_1 is 0 through 4, HOOC-$(CH_2)n_1$-COOH where n_1 is as defined above, HOOC-CH=CH-COOH and ϕ-COOH acids.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 95/08646

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY AND THERAPEUTICS, vol. 32, no. 5, 1994 MUNICH, DE, pages 223-230, J. FLEISHAKER ET AL 'Multiple Dose Tolerability and Pharmacokinetics of Tirilazad Mesylate at Doses of up to 10mg/Kg/Day Administered over 5-10 Days in Healthy Volunteers'	6-10
Y	see page 224, column 1, paragraph 1 see page 225; figure 1 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
8 November 1995	01. 12. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Watchorn, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHARMACEUTICAL RESEARCH, vol. 11, no. 2, February 1994 pages 341-344, J. FLEISHAKER ET AL 'Lack of Pharmacokinetic Interaction Between Cimetidine and Tirilazad Mesylate' cited in the application	6-10
Y	see page 341, column 1, paragraph 2 ---	1-10
X	THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 269, no. 1, April 1994 pages 145-150, P. BOMBART ET AL 'Protein Binding of Tirilazad (U-74006) in Human, Sprague-Dawley Rat, Beagle Dog and Cynomolgus Monkey Serum' cited in the application see page 146; figure 1B ---	6-10
Y	WO,A,87 01706 (UPJOHN CO) 26 March 1987 see page 90 - page 91; examples 83,109 ---	1-10
Y	CHEMICAL ABSTRACTS, vol. 085, no. 17, 25 October 1976 Columbus, Ohio, US; abstract no. 121285, KORNEL L ET AL 'Evidence for altered activities of steroid.DELTA.4-hydrogenase, 6-hydroxylase, and 20-reductase enzymes in essential hypertension: cause or effect?' see abstract & RES. STEROIDS , vol. 5, 1973 pages 413-427, ---	1-10
A	CHEMICAL ABSTRACTS, vol. 72, no. 5, 1970 Columbus, Ohio, US; abstract no. 21842, Y. HAMAMOTO ET AL '5-.beta.-1,9(11)-Pregnadiene-3,20-diones' page 343; see abstract & JP,A,44 027 721 (SHIONOGI AND CO., LTD) --- -/--	1-10

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 76, no. 1, 1972 Columbus, Ohio, US; abstract no. 336, E. GERHARDS ET AL 'Alkyl-Substituted Steroids. VII. Metabolism of 6-.alpha.-Fluoro-11-.beta.,21-dihydroxy-16 -.alpha.-methyl-pregna-1,4-diene-3,20-dion e (Fluocortolone) in Man. Isolation of 6-.beta.-Hydroxylated Metabolites' page 37; see abstract & ACTA ENDOCRINOL., vol. 68, no. 1, 1971 COPENHAGEN, pages 98-126, ---	1-10
P,X	CLINICAL PHARMACOLOGY AND THERAPEUTICS, vol. 56, no. 4, October 1994 ST. LOUIS, USA, pages 389-397, J. FLEISHAKER ET AL 'The Effect of Phenytoin on the Phamacokinetics of Tirilazad Mesylate in Healthy Male Volunteers' see page 389, column 2, paragraph 1 see page 390; figure 1 ---	6-10
P,A	DRUG METABOLISM AND DISPOSITION , vol. 23, no. 3, March 1995 BALTIMORE, USA, pages 383-392, WIENKERS L C ET AL 'In vitro metabolism of tirilazad mesylate in male and female rats: contribution of cytochrome P4502C11 and.DELTA.4-5.alpha.-reductase' see the whole document -----	1-10

1

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/US95/08646

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 11-15
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 11-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/US 95/08646

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8701706	26-03-87	EP-A-	0263213	13-04-88
		AU-B-	614661	05-09-91
		AU-B-	4080689	07-12-89
		AU-B-	593284	08-02-90
		AU-B-	6335686	07-04-87
		EP-A-	0238545	30-09-87
		FI-B-	94417	31-05-95
		JP-A-	5112597	07-05-93
		JP-B-	5035158	25-05-93
		JP-T-	63500868	31-03-88
		NO-B-	176762	13-02-95
		US-A-	5099019	24-03-92
		US-A-	5322943	21-06-94
		US-A-	5175281	29-12-92
		US-E-	RE35053	10-10-95
		US-A-	5268477	07-12-93
		US-A-	5380839	10-01-95
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		US-A-	5382661	17-01-95
		US-A-	5380841	10-01-95