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(54) Title: METHOD OF TREATING SMALLPOX AND MONKEYPOX

(57) Abstract: The present invention is a method of treating humans infected with the smallpox virus using a tricyclic amine, more particularly compounds selected from thioxanthenes such as chlorprothixene.

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METHOD OF TREATING SMALLPOX AND MONKEYPOX

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/501,912 entitled METHOD OF TREATING SMALLPOX AND MONKEYPOX, filed September 10, 2003, by Steven P. Radjenovich, the entire disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention includes a number of methods of treating humans infected with, or who may be come infected with, the smallpox or monkeypox virus using a tricyclic amine of formula (I).

2. Description of the Related Art

U.S. Patent 2,951,082 discloses substituted thiaxanthenes including the tricyclic amines (I) of the present invention as well as a process to prepare these compounds.

U.S. Patent 3,046,283 discloses various substituted thiaxanthenes and more specifically discloses 2-chloro-10-(3-dimethylaminopropylidene)thiaxanthene free base as well as the hydrochloride salt.

The Physicians Desk Reference (PDR) of 1990, the 44th Edition, discloses chlorprothixene which was marketed by Roche Pharmaceuticals under the trademark of TARACTAN. Chlorprothixene is 2-chloro-10-(3-dimethylaminopropylidene) thiaxanthene.

Smallpox is a very well known very contagious viral tragic disease for which there is no known recognized treatment. It is one of the most devastating, most widespread and most feared diseases to have impacted the human race in history. Other than avoidance, immunization is the only way a human can protect themselves from being infected upon exposure to the smallpox virus. During smallpox epidemics it was observed that milk maids were immune to smallpox. The reason is that by milking the cows the milk maids were exposed to cowpox which gave them immunity to the related smallpox virus, the variola virus. It was this knowledge that led to the smallpox vaccine. Because smallpox had been eradicated as a disease since 1977, babies born after 1977 were no longer vaccinated against smallpox and now the vast majority of the population has not been vaccinated. The concern today that the virus may be used an agent of bioterrorism.

Unfortunately, about 30 to about 50% of those who are not immunized against the smallpox virus and who get the disease, die. Chickenpox (varicella) and shingles (herpes zoster) are both caused by the varicella-zoster virus. Chickenpox is the acute invasive phase and shingles represents the reactivation of the latent phase which attacks the nerve roots.

www.authorsandexperts.com/search_detail.php?recordid=532 discloses a nontoxic homeopathic preventive for smallpox and smallpox vaccine reactions. Dr. Bill Gray advertises "homeopathy has proven completely safe and totally effective in preventing both adverse reactions to vaccines and smallpox itself." The identity of the homeopathic medicine is not disclosed.

The *Southern Medical Journal*, 67(7), 808 (July 1974) reported that in a clinical study with 30 patients who had shingles and were treated with chlorprothixene for herpes zoster neuralgia, the chlorprothixene was an effective analgesic agent in the management of herpes zoster neuralgia. There is no disclosure of chlorprothixene in treating the underlying disease, herpes zoster, causing the pain.

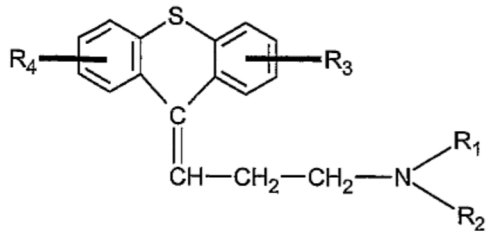
New England Journal of Medicine, 335(1), 32-42 (1966) discloses that spontaneous pain, pain provoked by trivial stimuli, and altered sensation accompany herpes zoster and may continue long after its characteristic rash has healed – a condition known as post herpetic neuralgia. The article states that tricycles antidepressant drugs are important components of therapy for post herpetic neuralgia. Because post herpetic neuralgia is the pain after the rashes of herpes zoster have healed, it is a method of treating pain, not a method of treating herpes zoster itself.

Pain, 5, 367-71 (1978) discloses that chlorprothixene (Taractan) can be used in treating post-herpetic neuralgia and other severe chronic pains. There is no disclosure of chlorprothixene in treating the underlying disease causing the pain.

Monkeypox virus is similar to the smallpox virus and appears to infect humans from small rodents.

SUMMARY OF INVENTION

Disclosed is a method of inhibiting an orthopox virus selected from the group consisting of the viruses that cause smallpox and monkeypox which comprises contacting the virus with an anti-orthopox viral effective amount of a tricyclic amine of formula (I)



(I)

and pharmaceutically acceptable salts, hydrates, metabolites and prodrugs thereof

where R_1 is C_1-C_3 alkyl;

where R_2 is C_1-C_3 alkyl;

and where R_1 and R_2 are taken with the nitrogen atom to which they are attached to form 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl and 4-morpholinyl;

where R_3 is selected from the group consisting of:

–F, -Cl, -Br, -I,

C_1-C_4 alkyl;

where R_4 is selected from the group consisting of:

-H,

–F, -Cl, -Br, -I,

C_1-C_4 alkyl.

These and other features, advantages and objects of the present invention will be further understood and appreciated by those skilled in the art by reference to the following specification and claims.

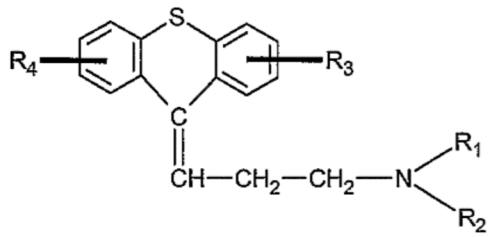
DETAILED DESCRIPTION OF THE INVENTION

The tricyclic amines of formula (I) which are useful in the methods of the present invention are known, see U.S. Patents 2,951,082 and 3,046,283.

The present invention includes different ways of using a tricyclic amine of formula (I) to treat/prevent smallpox and monkeypox in individuals, and in experimentation. It includes using a tricyclic amine of formula (I) to treat humans who are infected with the smallpox or monkeypox virus. Additionally, it includes using a tricyclic amine of formula (I) to treat/prevent smallpox in individuals exposed to the smallpox virus but in whom the virus is/can not be detected. Further, it includes using a tricyclic amine of formula (I) to prevent smallpox in individuals who have not been exposed to the smallpox virus but who are likely to be exposed to the smallpox virus. The invention also includes using a tricyclic amine of formula (I) *in vitro* and *in vivo* in non-human animals.

The orthopox family of viruses included both the virus which causes smallpox as well as the virus which causes monkeypox.

The present invention is a method of inhibiting an orthopox virus selected from the group consisting of the virus that causes smallpox and the virus which causes monkeypox which comprises contacting the virus with an anti-orthopox viral effective amount of a tricyclic amine of formula (I)



(I)

and pharmaceutically acceptable salts, hydrates, metabolites and prodrugs thereof

where R_1 is C_1-C_3 alkyl;

where R_2 is C_1-C_3 alkyl;

and where R_1 and R_2 are taken with the nitrogen atom to which they are attached to form 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl and 4-morpholinyl;

where R_3 is selected from the group consisting of:

–F, -Cl, -Br, -I,

C_1-C_4 alkyl;

where R_4 is selected from the group consisting of:

-H,

–F, -Cl, -Br, -I,

C_1-C_4 alkyl.

For the tricyclic amines (I) of the present invention, it is preferred that R_1 and R_2 are both C_1 alkyl. It is preferred that R_3 is -Cl and it is preferred that R_4 is –H.
It is preferred that the tricyclic amine (I) is chlorprothixene which is 2-chloro-10-(3-dimethylaminopropylidene)thiaxanthene. Chlorprothixene (I) has been marked by Roche Pharmaceuticals under the trademark of Taractan for the treatment of psychotic disorders. Chlorprothixene (I) was marketed in the free base form for oral tablet administration and as the hydrochloride and lactate salt for oral concentrate. Chlorprothixene (I) was also marketed as the hydrochloride salt for parenteral administration.

The tricyclic amines (I) are amines and as such form salts when reacted with acids. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds which are more water soluble and more crystalline. Pharmaceutically acceptable salts are preferred over the corresponding tricyclic amine free bases since they produce compounds which are more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J. Pharm.Sci.*, 66(1), 1, (1977). It is preferred that the salt be of hydrochloric or lactic acid.

The tricylic amines (I) can be administered either orally or parenterally by formulations known to those skilled in the art or readily prepared by those skilled in the art. The parenteral formulation is used for the more severe cases where obtaining a high blood level of the tricyclic amines (I) in a short time period is essential.

For oral solid dose administration the free base of the tricyclic amines (I) is suitable. For oral liquid (concentrate) administration the tricyclic amine (I) should be used as the pharmaceutically acceptable salt, preferably the hydrochloride and lactate salt. For parenteral administration the more water soluble hydrochloride salt is preferred.

The invention includes the situation where humans are or can be infected with either the smallpox or monkeypox virus.

The invention includes a method of inhibiting an orthopox virus where the inhibiting is treating a human who is infected with the smallpox or monkeypox virus and who is in need of treatment. This method includes two situations. First, where the human has clinical symptoms of smallpox or monkeypox and second, where the human does not have clinical symptoms of smallpox or monkeypox but the smallpox or monkeypox virus is detected in the human's blood. Both types of infected individuals, those exhibiting clinical symptoms and those not exhibiting clinical symptoms, but still infected, are treated according to the present invention.

The invention also includes a method of inhibiting an orthopox virus where the inhibiting is treating a human in which infection with the smallpox or monkeypox virus can not be detected but who has been exposed to the smallpox or monkeypox virus and who is in need of treatment. The fact that the smallpox or monkeypox virus is not detected in a person's blood does not mean that they are not infected, only that the virus can not be detected. Humans which have been exposed to the smallpox or monkeypox virus but who do not test positive for the smallpox or monkeypox virus should never-the-less be treated in the same manner and same way as those individuals who do not have any clinical symptoms but test positive for the smallpox or monkeypox virus. Because of the deadly nature of the diseases this preventative treatment is highly recommended. The treatment is administration of an anti-orthopox effective amount of a tricyclic amine of formula (I).

In addition, the invention includes a method of inhibiting an orthopox virus where the inhibiting is treating a human who is not vaccinated against smallpox prior to possible exposure to the smallpox or monkeypox virus and who is in need of such treatment. Usually the human will be exposed to the smallpox or monkeypox virus.

This is a method of preventing smallpox from developing in a person who will be exposed to either the smallpox or monkeypox virus. This method is useful when there is no time to vaccinate individuals. In the event of a bioterrorism attack with smallpox or monkeypox virus, the first responders, the medical personnel (physicians, nurses, pharmacists, physician's assistants, nurse's aids, etc), police, the armed forces and civilian support workers will probably be exposed to the smallpox or monkeypox virus before they have time to be vaccinated and full immunity is permitted to develop. These responders in most cases would not have time to obtain a vaccination and give the vaccination sufficient time to permit full immunity to develop (about 30 days) before being exposed to the

orthopox virus. In that situation, the first responders should be treated with an anti-orthopox effective amount of a tricyclic amine of formula (I) to prevent a smallpox or monkeypox infection. This is a prophylactic method of treatment rather than waiting for the individual to become infected and then treating the individual. Using this method the anti-orthopox viral effective amount is the same and is administered in the same way as to treat an infected person. The difference is that the treatment is administered before the individual is infected with the smallpox or monkeypox virus.

Since young children and large adults both can get smallpox and monkeypox, the anti-orthopox viral effective amount of the tricyclic amines (I) varies considerably. For young children about 10 mg three to four times daily may be sufficient. A useful anti-orthopox viral effective amount to treat a human is from about 30 mg/day to about 3,000 mg/day. It is preferred that the anti-orthopox viral effective amount to treat a human is from about 100 mg/day to about 1,000 mg/day, more preferred is where the anti-orthopox viral effective amount to treat a human is from about 200 mg/day to about 800 mg/day. The daily dose can be administered in divided doses, preferably two to four times daily. If a sustained release form of the tricyclic amine (I) is used, the tricyclic amine can be administered once or twice daily. Dosing is continued for at least 10 days or until the last crop of infestation is crusted.

The exact dosage and frequency of administration depends on the particular tricyclic amine (I), 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 the tricyclic amine (I) in the patient's blood and/or the patients response to the condition being treated. Care should be used in administering steroids to individuals which may be infected with or who may become infected with the smallpox or monkeypox virus and be treated by the method of the present invention.

Humans infected with the smallpox or monkeypox virus, or who may become infected, may or may not have been immunized against the smallpox virus. If not immunized, there is no protection against smallpox or monkeypox virus other than the tricyclic amines (I) of the present invention. In addition, humans who have been immunized against the smallpox virus but less than about 30 days ago or more than about 31 years ago

can become infected. The reason is that once immunized against the smallpox virus, it takes the immunization about 7-10 days to produce some immunity and full immunity in 21-30 days. Therefore, if an individual is immunized against the smallpox virus but is exposed to the smallpox or monkeypox virus before immunization is complete, that individual will likely become infected, and if infected, and can be treated by the method of the invention. In addition, since it was believed that smallpox as a disease had been eradicated from the earth, smallpox vaccinations were stopped around 1977. Those individuals vaccinated in 1976, or before, are 27 years or older, some in their 70s, 80s and 90s. For individuals who have been immunized more than about 31 years ago, the vaccination protection has decreased and these vaccinated individuals can now become infected. These previously immunized individuals whose immunity has decreased to the point that the immunity is not now effective protection and who will probably get smallpox or monkeypox if exposed to the corresponding orthopox virus, can be treated by the method of the present invention.

The invention also includes a method for inhibiting the smallpox virus both *in vitro* and *in vivo* for non-humans. This method inhibits the smallpox or monkeypox virus when the smallpox or monkeypox virus is not in a human which comprises: (1) contacting the smallpox virus with a tricyclic amine (I) and pharmaceutically acceptable salts thereof. The method inhibits the smallpox virus *in vitro* when the smallpox virus is contacted with a tricyclic amine (I) or pharmaceutically acceptable salt thereof. Typically this would be an assay or laboratory screening. In this situation the smallpox virus is contacted with a tricyclic amine (I) where the concentration of the tricyclic amine (I) is from about 1mg/ml to about 900 mg/ml, alternatively, the concentration of the tricyclic amine (I) is from about 50 mg/ml to about 750 mg/ml. The smallpox or monkeypox virus can be inhibited in animal models, *in vivo* testing, when test animals are infected with the smallpox or monkeypox virus and then the tricyclic amines (I) are administered to the test animal. Suitable test animals include monkeys and rodents selected from the group consisting of rats, prairie dogs (*Ctbints sp.*), squirrel, mice, rabbits.

The method of treating humans infected with the monkey pox virus is performed in the same manner and same way as for smallpox as is known to those skilled in the art. Those skilled in the art who know how to treat or prevent infections of smallpox would know how to treat or prevent infections of monkeypox.

DEFINITIONS AND CONVENTIONS

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

DEFINITIONS

Treating or treatment as used in this invention, with regard to humans infected with the smallpox virus, does not require a cure, just an improvement in the patient's condition over what the patient's condition would have been absent administration of the tricyclic amine (I).

Treating or treatment as used in this invention, with regards to humans in which infection with the smallpox virus can not be detected but who have been exposed to the smallpox virus, refers to the administration of the tricyclic amine (I) to the patient, not any result obtained.

Inhibiting as used in this invention means reducing or a reduction in the smallpox virus's ability to infect a human, it does not in any way refer to or imply the mechanism by which it is done. Inhibiting just refers quantitatively to the smallpox virus's reduced ability to infect a human.

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.

Taractan is the trademark for the generic pharmaceutical compound, chlorprothixene, which is chemically known as 2-chloro-10-(3-dimethylaminopropylidene)thiaxanthene.

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 40 Year Old Non-Smallpox Immunized Male

A forty-year-old 72 kg non-smallpox immunized male who has been exposed to smallpox within the past 48 hr but shows no active signs of the disease yet. The patient is given 50 mg of chlorprothixene four times a day until the last crop is crusted.

EXAMPLE 2 66 Year Old Previously Smallpox Immunized Female

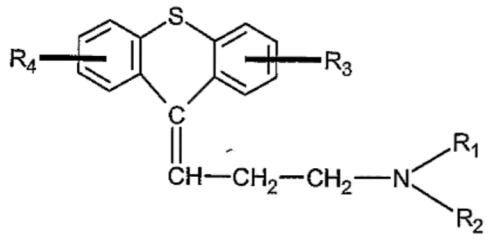
A sixty-six year-old white 61 kg female who has had previous smallpox immunizations but not since the 70's has been exposed to smallpox and is showing early signs of the disease. She is treated with 100 mg of chlorprothixene lactate by mouth three times daily for 4 days. Since the disease does not seem to be lessening, the dose is increased to 200 mg four times daily until the last crop is crusted.

EXAMPLE 3 7 Year Old Non-Smallpox Immunized Child

A seven-year-old 11 kg child was exposed to smallpox but has no physical manifestations. The child is started on 10 mg four times a day and after 3 days is increased to 25 mg a day for 3 days. Since the physical manifestations are increasing, the child is started on IV chlorprothixene hydrochloride 300 mg/day until the symptoms are decreasing. The patient is then returned to oral dosing until the last crop is crusted.

ENUMERATED EMBODIMENTS

1. Use of a tricyclic amine of formula (I)



(I)

and pharmaceutically acceptable salts thereof

where R_1 is C_1-C_3 alkyl;

where R_2 is C_1-C_3 alkyl;

and where R_1 and R_2 are taken with the nitrogen atom to which they are attached to form 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl and 4-morpholinyl;

where R_3 is selected from the group consisting of:

–F, -Cl, -Br, -I,

C_1-C_4 alkyl;

where R_4 is selected from the group consisting of:

-H,

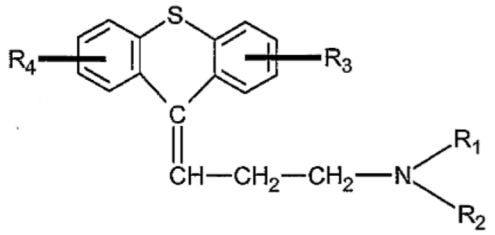
–F, -Cl, -Br, -I,

C_1-C_4 alkyl for the manufacture of a medicament for use in inhibiting an orthopox virus selected from the group consisting of the viruses that cause smallpox and monkeypox.

The above description is considered that of the preferred embodiment only. Modifications of the invention will occur to those skilled in the art and to those who make or use the invention. Therefore, it is understood that the embodiment shown and described above is merely for illustrative purposes and not intended to limit the scope of the invention, which is defined by the following claims as interpreted according to the principles of patent law, including the doctrine of equivalents.

CLAIM

1. A method of inhibiting an orthopox virus selected from the group consisting of the viruses that cause smallpox and monkeypox which comprises contacting the virus with an anti-orthopox viral effective amount of a tricyclic amine of formula (I)



(I)

and pharmaceutically acceptable salts, hydrates, metabolites and prodrugs thereof

where R_1 is C_1-C_3 alkyl;

where R_2 is C_1-C_3 alkyl;

and where R_1 and R_2 are taken with the nitrogen atom to which they are attached to form 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl and 4-morpholinyl;

where R_3 is selected from the group consisting of:

–F, -Cl, -Br, -I,

C_1-C_4 alkyl;

where R_4 is selected from the group consisting of:

-H,

–F, -Cl, -Br, -I,

C_1-C_4 alkyl.

2. A method of inhibiting an orthopox virus according to claim 1 where R_1 and R_2 are both C_1 alkyl.

3. A method of inhibiting an orthopox virus according to claim 1 where R_3 is –Cl.

4. A method of inhibiting an orthopox virus according to claim 1 where R_4 is –H.

5. A method of inhibiting an orthopox virus according to claim 1 where the tricyclic amine (I) is chlorprothixene.

6. A method of inhibiting an orthopox virus according to claim 1 where the pharmaceutically acceptable salt is selected from the group consisting of salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic.

7. A method of inhibiting an orthopox virus according to claim 6 where the pharmaceutically acceptable salt is the salt of the following acids hydrochloric or lactic.

8. A method of inhibiting an orthopox virus according to claim 1 where the tricyclic amine (I) is administered orally.

9. A method of inhibiting an orthopox virus according to claim 1 where the tricyclic amine (I) is administered parenterally.

10. A method of inhibiting an orthopox virus according to claim 1 where the orthopox virus is the virus which causes smallpox.

11. A method of inhibiting an orthopox virus according to claim 1 where the orthopox virus is the virus which causes monkeypox.

12. A method of inhibiting an orthopox virus according to claim 1 where the inhibiting is treating a human who is infected with the smallpox or monkeypox virus and who is in need of treatment.

13. A method of inhibiting an orthopox virus according to claim 12 where the human has clinical symptoms of smallpox or monkeypox.

14. A method of inhibiting an orthopox virus according to claim 12 where the human does not have clinical symptoms of smallpox but the smallpox virus is detected in the human's blood.

15. A method of inhibiting an orthopox virus according to claim 1 where the inhibiting is treating a human in which infection with the smallpox or monkeypox virus can not be detected but who has been exposed to the smallpox virus and who is in need of treatment.

16. A method of inhibiting an orthopox virus according to claim 1 where the inhibiting is treating a human who is not vaccinated against smallpox prior to possible exposure to the smallpox or monkeypox virus and who is in need of such treatment.

17. A method of inhibiting an orthopox virus according to claim 16 where the human is exposed to the smallpox or monkeypox virus.

18. A method of inhibiting an orthopox virus according to claim 1 where the anti-orthopox viral effective amount to treat a human is from about 30 mg/day to about 3,000 mg/day

19. A method of inhibiting an orthopox virus according to claim 18 where the anti-orthopox viral effective amount to treat a human is from about 100 mg/day to about 1,000 mg/day.

20. A method of inhibiting an orthopox virus according to claim 19 where the anti-orthopox viral effective amount to treat a human is from about 200 mg/day to about 800 mg/day.

21. A method of inhibiting an orthopox virus according to claim 1 where the inhibiting is in a human who has not been vaccinated against the smallpox virus.

22. A method of inhibiting an orthopox virus according to claim 1 where the inhibiting is in a human who has been vaccinated against the smallpox virus but less than about 30 days ago or more than about 31 years ago.

23. A method of inhibiting the orthopox virus according to claim 1 where the virus is not in a human.

24. A method of inhibiting an orthopox virus according to claim 23 where the contacting takes place *in vitro*.

25. A method of inhibiting an orthopox virus according to claim 23 where the concentration of the tricyclic amine (I) is from about 1 mg/ml to about 900 mg/ml.

26. A method of inhibiting an orthopox virus according to claim 25 where the concentration of the tricyclic amine (I) is from about 50 mg/ml to about 750 mg/ml.

27. A method of inhibiting an orthopox virus according to claim 23 where the contacting takes place *in vivo* but not in a human.

28. A method of inhibiting an orthopox virus according to claim 23 where the anti-orthopox effective amount of the tricyclic amine (I) during contacting is from about 4 mg/kg to about 150 mg/kg.

29. A method of inhibiting an orthopox virus according to claim 23 where the inhibiting takes place in a monkey or groundhog.