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(57) Abstract

A method of inhibiting viruses in which a virus is contacted with diamondoid alcohol, ketone, keton derivative, adamantyl amino acid, quaternary salt or combinations thereof which have antiviral properties. These diamondoid derivatives are shown to have antiviral activity against HIV.
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DIAMONDOD DERIVATIVES FOR PHARMACEUTICAL USE

This invention relates to adamantane and diadamantane derivatives useful as pharmacological agents for use in pharmaceutical compositions such as antivirals.

Numerous adamantane-based compounds have been tested for their activity against a number of infectious agents such as bacteria, viruses and as treatments against cancer and parkinson's disease, as well as a means of treating cardiac, circulatory and vascular disease, hypertension, depression and drug-induced extrapyramidal reactions. For a review on this topic, see Chapter 7 in Adamantane, The Chemistry of Diamond Molecules, R.C. Fort, Jr., Marcel Dekker, Inc., 1976.

Adamantane, also known as tricyclo-[3.3.1.1^3,7] decane, is a polycyclic alkane with the structure of three fused cyclohexane rings. The ten carbon atoms which define the framework structure are arranged in an essentially strainless manner thereby giving a very stable backbone for the addition of a variety of moieties. Four of these carbon atoms, the bridgehead carbons, are tetrahedrally disposed about the center of the molecule. The other six (methylene carbons) are octahedrally disposed. Because of the particular reactivity of adamantane, functional groups have been readily introduced at the bridgehead 1-, 3-, 5-, 7- positions of adamantane. U.S. Patent Nos. 5,019,660 to Chapman and Whitehurst and 5,053,434 to Chapman teach diamondoid compounds which bond through the methylene positions of various diamondoid compounds. For a survey of the chemistry of diamondoid molecules, see Adamantane, The Chemistry of Diamond Molecules, Raymond C. Fort, Marcel Dekker, New York, 1976. For synthesis methods for adamantanes, see Paul Schleyer, Cage Hydrocarbons, George A. Olah, ed., Wiley, New York, 1990.

The IUPAC numbering system for adamantane and diadamantane is shown below.
These have been called diamondoid compounds because their structures are part of the diamond lattice.

Certain derivatives of adamantane particularly those with amino substitutions at the (1-) position have been found to demonstrate activity against influenza and herpes, as well as against certain cancers such as angiocarcinoma and pancreatic carcinoma.

U.S. Patent No. 3,152,180 to Haaf discloses N-tertiary alkyl amines and amides as intermediates for pharmaceutical use. For example, N-(adamantyl-1)-formamide is disclosed.

U.S. Patent No. 3,342,863 to Hermann discloses certain lower alkyl 1-amino adamantane oxides having the formula

\[
\text{1-Ad} - \text{N} - R_1 ^{\ominus} \quad R_2
\]

where \( R_1 \) and \( R_2 \) may be \( \text{C}_{1-12} \) alkyl, as useful antiviral agents and antioxidants.

U.S. Patent No. 3,352,912 to Prichard discloses (1-) substituted adamantane (\( \text{C}_{10} \)) derivatives having an aminomethyl or N-substituted aminomethyl group attached to a bridgehead (1-) nuclear carbon atom of adamantane and also (3-) substituted tricyclo [4.3.1.1^{3,6}] undecanes (\( \text{C}_{11} \)).

The compounds are used as antiviral agents.

British Patent No. 1,063,365 describes adamantane substituted at the (1-) position with a primary or secondary amino group for use against swine influenza.

 adamantane substituted at the (1-), (3-), (5-) and (7-)
 positions with hydrogen, methyl, or (CH₃)ₙCH(NH₂)CO₂H and
 having the formula

\[ \text{R, } R_1 = \text{H, Me} \]
\[ (\text{CH}_3)_n\text{CH(NH}_2\text{)}\text{CO}_2\text{H} \]
\[ R_2 = \text{H, Me, CH(NH}_2\text{)}\text{CO}_2\text{H} \]

The products were tested using A- and Sindbis - type
viruses. The results are not described in the English
Abstract.

More recently, U.S. Patent No. 5,221,693 to Shetty
discloses bis-adamantane based compounds of the formulas

I) \[ Z-\text{C-NH-C-NH-} (\text{CH}_3)_n\text{-NH-C-NH-C-Z} \]
\[ \text{J-N J-N J-N J-N} \]

or

II) \[ Z-\text{C-NH-C-NH-C*-} (\text{CH}_3)_n\text{-NH-C-NH-C-Z} \]
\[ \text{J-N J-N A J-N J-N} \]

in which Z is an adamantane group. All of the compounds
require two separate 1-adamantany1 moieties. The compounds
are described as having antimicrobial and antiviral uses
including against gram-positive and gram-negative bacteria,
fungi, yeasts and enveloped viruses such as herpes and
retroviruses.

A survey of adamantane compounds which have been tested
for pharmacological activity is presented in Adamantane,
The Chemistry of Diamond Molecules, Raymond C. Fort, Jr.,
Marcel Dekker, New York, 1976. Described compounds are
adamantanes which are generally amino-substituted at the 1
or 2 position. The 1-aminoadamantanes which include
primary and secondary amino functional groups were effective against certain viruses, such as influenza A, B, rous sarcoma, esh sarcoma, sendai, Newcastle, herpes, vaccinia and parainfluenza viruses. The survey discloses that adamantan which was amino-substituted with NHCSNHR at the (2-) position was modestly effective against herpes, vaccinia and Newcastle virus. 3-R-Homoadamantane, R = CH₃NH₂, CH(CH₃)NH₂ or C(CH₃)₂NH₂, had activities similar to 1-aminoadamantan. However, 1-aminoadamantanes which were also substituted at the (3-) position with R = CO₂H or NH₂ showed no activity; R = OH showed slight activity. 3-CO₂H-1-AdCH₂NR₂ also showed no antiviral activity, while 3-R-1-AdNH₂, R = CH₃ or Br showed significant activity.

It is apparent from this survey that antiviral activities of adamantane have derived primarily from certain amino substitutions at the 1 or 2 positions of adamantane or 3-substituted homoadamantanes. It also appears that only analogues with amino substitutions at the (1-) position gave predictable activity.

German Patent DE 3921062 describes using 1-adamantamine hydrochloride in combination with AZT for therapy and prophylaxis of retroviruses such as HIV-1.

In the design of antiviral agents, viruses are targeted at steps in their life cycles. Attempts have been made to interrupt replication of viral nucleic acids in the infected cell or to interrupt the synthesis of viral proteins. However, viral multiplication must be inhibited without the undesirable side effect of damaging the host cells (cytopathic effect). The majority of anti-retrovirals and antivirals have been analogs of deoxyribonucleosides such as AZT, ddI and ddC which are used for HIV infections and which interfere with the synthesis of viral nucleic acids.

Amantadine at higher concentration (> 0.5 mM), non-specifically inhibits viral entry into the cell by altering the pH of the endocytic vesicle. At lower concentration
(about 5μM), amantadine exhibits a selective strain-specific inhibition of virus assembly (See, e.g., Hay, A.J. and Zambon, M.C., "Multiple Actions of Amantadine Against Influenza Viruses", in Dev. Mol. Virol. 1984, 4 (Antiviral Drugs and Interferon: The Molecular Basis of Their Activity), Becker, Y., ed., 1984, 301-15. 1-Aminoadamantane hydrochloride (amantadine hydrochloride) is available commercially as an antiviral under the name Symmetrel and is used in the treatment and prevention of influenza A infections. The (1-) position of adamantane has also been substituted with -CH(CH₃)NH₂. The resulting compound is available commercially under the name Rimantadine which is also used in the treatment and prevention of influenza A.

Presently a great deal of research is focused on finding active agents against HIV infection. These agents are also usually targeted at a specific step in the complex life cycle of the virus. By interrupting a specific step in viral replication using therapeutic drugs, it is hoped that symptoms from infection can be at least delayed if not prevented. Most clinical successes to date have focused on the point in the viral life cycle where the genetic material of HIV (RNA) is reverse transcribed into DNA, which then infiltrates the host cell's genes. The drugs AZT, ddI and ddC work in this manner. Other methods for halting the life cycle target the HIV enzyme protease, which is required for assembling newly made HIV particles, or other proteins which govern replication.

Thus far the most effective compounds which have been approved to treat HIV infection act at the reverse transcription step. Presently, there is a need to find therapeutic agents which act at different stages of the viral life cycle. It is hoped that a combination of drugs acting at different steps of the viral life cycle would overcome the development of resistance by the virus. This type of combination drug therapy has been used successfully
against intractable bacterial infections such as tuberculosis.

According to the present invention, certain diamondoid derivatives have been found to act at more than one step, that is, either early in the life cycle, or in the later stages of the virus life cycle. These compounds also differ from previously used antiviral amantadine derivatives in that the new compounds have different substituted sites and different substituents at these sites in their structures. Particularly effective compounds in the present invention are diamondoid ketones. Previously, this class of compounds has not been known to have any pharmacological activity whatsoever.

The invention resides in a pharmaceutical composition comprising a compound of formula I, formula II or combinations thereof and a pharmaceutically acceptable carrier or diluent:

\[
\text{formula I}
\]

wherein

Y is a bond, \(\text{CH}_2\), oxygen, sulfur, sulfoxide, sulfone or NH;

\(R_1, R_4, R_6\), and \(R_{10}\) are individually hydrogen, hydroxyl, lower alkyl of 1 to 8 carbon atoms, OZ where Z is lower alkyl of 1 to 8 carbons, COQ where Q is hydrogen or lower alkyl of 1 to 8 carbons, or \(\text{OSO}_2\text{H}\);

\(R_2, R_3, R_5, R_7, R_9, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}\) and \(R_{16}\) are individually hydrogen, hydroxyl, lower alkyl of 1 to 8 carbons, double-bonded oxygen, COQ where Q is hydrogen or lower alkyl of 1 to 8 carbons; OCQ' where Q' is hydrogen, lower alkyl of 1 to 8 carbons or aryl; \(\text{OSO}_2\text{H}, -\text{D} \left(\text{CH}_2\right)_n -\text{D}\)
where \( n \) is 2 or 3 and \( D \) is oxygen or sulfur; COOQ where \( Q \) is hydrogen or lower alkyl of 1 to 8 carbons, \((OZ)_2\) where \( Z \) is lower alkyl of 1 to 8 carbons;

\[ \overset{0}{S} = N-Z' \] where \( Z' \) is hydrogen, \( \text{NH}_2, \text{OH}, -\text{NH}-\text{C}-\text{NH}_2 \) or \( -\text{NH}-\text{C}=\text{NH}_2 \);

\( \text{NHQ}'' \) where \( Q'' \) is lower alkyl of 1 to 5 carbons; an amino acid, \( \text{SH} \), or a moiety of formula A

\[ \begin{align*}
+ & \quad R_a \\
& \quad R_b \\
& \quad R_c \\
\end{align*} \quad X^- \]

formula A

wherein \( R_a \) is hydrogen or lower alkyl of 1 to 8 carbons; \( R_b \) is lower alkyl of 1 to 8 carbons; \( R_c \) is hydrogen or lower alkyl of 1 to 8 carbons; \( X^- \) is a counterion; and \( R_{1-16} \) are not all hydrogen;

**formula II**

wherein \( Y \) is a bond, \( \text{CH}_2 \), oxygen, sulfur, sulfoxide, sulfone or \( \text{NH} \); \( R_{17}, R_{18}, R_{21}, R_{24}, R_{25}, R_{28}, R_{31} \) and \( R_{32} \) are individually hydrogen, hydroxyl, lower alkyl of 1 to 8 carbons, \( OZ \) where \( Z \) is lower alkyl of 1 to 8 carbons, COQ where \( Q \) is hydrogen or lower alkyl of 1 to 8 carbons,

\[ \begin{align*}
& \quad \text{OSO}_2\text{H}, \text{NH}_2, \text{NHR'}, \text{NR'R''}, \text{NR'R''R'''}, \\
& \quad \text{SH}, \text{aryl}, \text{furyl or pyridyl}; \\
& \quad \text{R}_{19}, \text{R}_{20}, \text{R}_{22}, \text{R}_{23}, \text{R}_{26}, \text{R}_{27}, \text{R}_{29}, \text{R}_{30}, \text{R}_{33}, \text{R}_{34}, \text{R}_{35} \text{ and } \text{R}_{36} \\
& \quad \text{are individually hydrogen, hydroxyl, double-bonded oxygen, COQ where } Q \text{ is hydrogen or lower alkyl of 1 to 8 carbons,} \\
& \end{align*} \]
OCOQ' where Q' is hydrogen, lower alkyl of 1 to 8 carbons or aryl; OSO₂H, -D(CH₂)ₙ

where n is 2 or 3 and D is oxygen or sulfur, COOQ where Q is hydrogen or lower alkyl of 1 to 8 carbons, (OZ)₂ where Z is lower alkyl with 1 to 8 carbons, -NZ' where Z' is hydrogen, NH₂, OH, -NH-C-NH₂ or -NH-C-NH₂; NH₂, NHR, NR'R''

where R' and R'' are individually lower alkyl of 1 to 8 carbons; SH, an amino acid or a moiety having formula B or formula C

\[
\begin{align*}
\text{formula B} & \quad \text{formula C} \\
\begin{align*}
R_d & \quad + \quad R_d \\
R_e & \quad \text{or} \quad N-R_e \\
R_f & \\
\end{align*}
\end{align*}
\]

wherein R_d is hydrogen or lower alkyl of 1 to 8 carbons; + R_e is \((\text{CH}_2)_n N(\text{CH}_3)_m\) \((X^-)\) where n = 2 or 3 and X' is a counterion; or lower alkyl of 1 to 8 carbons, R_f is lower alkyl of 1 to 8 carbons; \(R_{17-36}\) are not all hydrogen; and wherein all substituents in formula I and formula II contribute to a stable molecule. The various alkyl groups described in formula I and formula II may be branched or unbranched, and typical examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, isobutyl, penty1, hexyl, hepty1 and octyl.

Aryl groups are typically phenyl but also may be other aryl groups, for example, naphthyl, pyrrolyl, furanyl, thiophenyl, and pyridyl. The aryl group may be further substituted, e.g. by an inorganic such as halo, or an organic such as an alkyl group of 1 to 8 carbons.

As used herein, the term "individually" means each radical in a grouped set of radicals can be the same or different.
All substituents contribute to a stable molecule so that, e.g., $R_1$ and $R_2$ cannot both be double bonded oxygen.

As used herein diamondoid means adamantane or diadantane.

The compounds of formula I and formula II are used to inhibit activity or virus entry into cells or replication of a virus by contacting an effective antiviral amount of the compound with a virus, a virus-infected cell or virus-infectable cell so that a virus-caused cytopathic effect or viral replication is avoided.

The compounds of formula I and formula II have antiinfective activity and they may be used for the preparation of pharmaceutical formulations and in kits.

The composition of the invention is effective in inhibiting retroviruses including lentiviruses and the oncoviroidae. The invention is particularly effective against human retrovirus of the Lentiviral family, Human Immunodeficiency Virus (HIV).

Advantageously, antiviral activity has been shown at more than one stage of the viral life cycle; and antiviral activity has been shown against an AZT resistant strain of HIV as well as against a primary clinical isolate of the virus.

Compounds useful herein are described by formulae I and II above. Examples of compounds having formula I are hydroxy diamondoids, i.e., diamondoid alcohols or diamondoid polyols, diamondoid quaternary ammonium compounds, diamondoid ketones and their carbonyl derivatives, and diamondoid amino acids, for example:

![Chemical structure](image)

$\text{C}_{10}\text{H}_{16}\text{O}_4$, $1,3,5,7$-adamantanetetraol

$(1,3,5,7$-tetrahydroxytricyclo$[3.3.1.1^{3,7}]$decane)
and

\[ \text{C}_{12}\text{H}_{26}\text{O}_2 \]
1,3-dihydroxy-5,7-dimethyladamantane
(1,3-dihydroxy-5,7-dimethyl) tricyclo [3.3.1.1\(^3,7\)] decane
(1,3-Adamantanediol-5,7-dimethyl)
(5,7-dimethyl-1,3-adamantanediol).

Compounds of formula I also include 2-adamantyl amino acids such as

\[ \text{C}_{12}\text{H}_{19}\text{NO}_2 \]
N-2-adamantyl glycine
(N-2-adamantylamino) acetic acid

and diamondoid ketones such as

\[ \text{C}_{10}\text{H}_{12}\text{O}_2 \]
2,4-adamantanedione
(tricyclo[3.3.1.1\(^3,7\)]decane-2, 4-dione)

and carbonyl derivatives of diamondoid ketones such as
C₁₂H₁₈O₃  4(α)-hydroxy-2-adamantanone
ethylene glycol ketal
(Spiro[1,3-dioxolane-2,2’-tricyclo
[3.3.1.1³,⁷] decane
-4’-ol, 1’α,3’β,4’α,5’α,7β

Examples of compounds having formula II are

\[
\begin{align*}
\text{CH}_3 & \quad \text{or} \quad \text{CH}_3 \\
\text{N}^+ & \text{-} \text{(CH}_2\text{)}_3 \text{-} \text{N}^+ \text{-} \text{CH}_3 \quad \text{(II')}
\end{align*}
\]

and

C₂₂H₃₆N₂I₂  N-3-diamantyl-N,N,N',N',N'-pentamethyl propane
1,3-bis ammonium diiodide

C₁₄H₁₉O  3-diamantanone
(octahydro-3,5,1,7-[1.2.3.4]butanetetrayl
naphthalene-2(1H)-one

Preferred compounds are diamondoid ketones.
The invention also relates to the use of the compounds of
formulas I and II and their pharmaceutically
acceptable salts when appropriate for the preparation of
pharmaceutical formulations. The salts may be prepared
using simple acid-base reactions.
The pharmaceutical composition may be administered in any number of acceptable and physiologically tolerable ways such as orally, subcutaneously, percutaneously, intramuscularly, by suppository, intravenously, intranasally (inhaled), or intraarticularly or by external application including nebulization (spraying).

The pharmaceutical compositions can be formulated and prepared by established pharmaceutical procedures into composition for administration. The compounds may be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carriers which do not deleteriously interact with the active compounds.

The compounds of this invention possess valuable pharmacological properties for both human and veterinary medicine. The compounds display antiviral and antitumor effects and are useful particularly in the prevention and chemoprophylaxis of viral illnesses. The compounds are also useful in the treatment of bacterial and mycotic infections. These compounds are particularly useful as antivirals.

In addition, the compounds can be used in in vitro diagnostics (e.g., in an assay for renin, bacteria, virus, etc.).

They can be employed in admixture with carriers, germicides, fungicides, soaps, and in spermicides and on condoms and birth control devices, etc. and used in antiseptic solutions and the like, particularly in conjunction with hospital housekeeping procedures, e.g., to combat HIV. The compounds can be applied on syringes/needles, containers such as specimen containers, gowns, gloves, etc., and in biologicals and in blood products such as clotting factors for clinical use.

The compounds of the invention are also useful as intermediates to synthesize other pharmaceuticals such as functionalized triamines, tetraamines, and higher
functionalized diamondoid-containing amines and their derivatives.

A kit for use in determining the presence of virus, particularly retrovirus and more particularly, Human Immunodeficiency Virus (HIV) or Human T-cell Leukemia Virus (HTLV), which are implicated in Acquired Immunodeficiency Syndrome (AIDS), includes a compound of formula I or formula II or combinations thereof. The virus causes cells grown in tissue culture to demonstrate a cytopathic effect and to form syncytia. A syncytium is a multinucleated cell formed by cytoplasmic fusion, without nuclear fusion, of a number of individual cells. Various dye uptake tests, immunoassays and reverse transcriptase assay can also be used to test for virus. Therefore, the compounds of formula I and formula II can be used in a microtiter infection assay by screening for a known viral effect such as the formation of syncytia or, e.g., using a dye uptake test.

The pharmacological compounds of this invention are generally administered to animals, including mammals, fish, reptiles, and avians, more preferably to mammals including humans, primates, livestock, cattle, horses, household pets including cats and dogs; and avians including poultry.

The pharmacologically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, e.g., mammals including humans.

The compounds of this invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral) or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates
such as lactose, amylose, or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, merely to name a few. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifier, salts for influencing osmotic pressure, buffers, coloring, flavoring, and/or aromatic substances and the like which do no deleteriously react with the active compounds. They can also be combined where desired with other agents, e.g. vitamins.

For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants including suppositories. Ampoules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules. A syrup, elixir, or the like can be used wherein a sweetened vehicle is employed. Nebulizers and inhalation aerosols may also be used.

Sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable coating, e.g., by microencapsulation, multiple coatings, etc. It is also possible to freeze-dry the new compounds and use the lyophilizates obtained, for example, for the preparation of products for injection.

For topical application, there are employed as nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to transdermal patches, solutions, suspensions, emulsions,
creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservations, stabilizers, wetting agents, buffers, or salts for influencing osmotic pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with pressurized volatile, normally gaseous propellant, e.g., a freon.

Generally the compounds of this invention are dispensed in unit dosage from comprising from 10 to 1000 mg in a pharmaceutically acceptable carrier per unit dosage. They are incorporated in topical formulations in concentrations from 0.01 to 3 weight percent.

The dosage of the compounds according to this invention generally is from 0.1 to 100 mg/kg day, preferably 0.1 to 20 mg/kg day when administered to patients, e.g., humans as an antiviral.

It will be appreciated that the actual preferred amounts of active compound in a specified case will vary according to the specific compound being utilized, the particular compositions formulated, the mode of the application, and the particular situs and organism being treated. Dosages for a given case can be determined using conventional considerations, e.g., by customary comparison of the differential activities of the subject compounds and of a known agent, e.g., by means of an appropriate conventional pharmacological protocol.

The treatment of viral disease has been approached by inhibiting adsorption or penetration of virus into the cells, inhibiting intracellular processes which lead to the synthesis of viral components, or inhibition of release of newly synthesized virus from the infected cell. The inhibition of one or more of these steps depends on the chemistry or mode of action of the virus.
Viruses share certain common characteristics: they consist of a nucleic acid genome surrounded by a protective protein shell (capsid) and the protein shell may be enclosed in an envelope which further includes a membrane. Viruses can multiply only inside living cells after the virus has infected the cell and the viral genome has been introduced into the cell. Animal viruses may differ in their types of nucleic acid which may be double-stranded DNA, single-stranded DNA, single-strand positive RNA, single-strand negative RNA, and double-stranded RNA.

Double-strand DNA viruses include Hepadna viruses such as the virus causing hepatitis B (Dane particle); Poxviridae such as the viruses causing smallpox (variola), swinepox, rabbit myxoma and orf; Herpesviridae such as the viruses causing herpes simplex (HSV-1 and HSV-2), cytomegaly, viral lymphoproliferative disease, Burkitt lymphoma, nasopharyngeal carcinoma in China, infectious mononucleosis (Epstein-barr) and chickenpox (varicella-zoster); and Adenoviridae such as adenovirus causing acute respiratory tract disease.

Single strand DNA viruses include Papoviridae which are non-enveloped viruses causing human warts (papillomavirus) and JC virus causing progressive multifocal leukoencephalopathy.

Positive-strand RNA viruses include Retroviridae such as the viruses causing human T-cell leukemia (HTLV-1 and HTLV-II) and Acquired Immunodeficiency Disease (AIDS) (HIV-1 and HIV-2). The HIV viruses have many characteristic of lentiviruses.

Positive-strand RNA viruses also include Picornaviridae such as the enteroviruses causing polio, Coxsackie virus infections and hepatitis A.

Negative-strand RNA viruses include Orthomyxoviridae such as the viruses causing influenza A, B and C;

Paramyxoviridae such as the viruses causing mumps, measles, parainfluenza, and respiratory syncytial disease
(pneumovirus); and Rhabdoviridae such as the virus causing rabies.

Double-strand RNA viruses include Reoviridae such as the viruses causing certain gastroenteritis (rotavirus).


The treatment of viral disease by chemical drugs has targeted inhibition of intracellular metabolic processes which lead to the synthesis of viral constituents or release of virus from the host cell (late); and inhibition of absorption or penetration of the virus into the host cell or integration of the viral genome into that of the host cell (early).

The invention is particularly concerned with pharmaceutical preparations which can be used in the treatment of HIV infection and AIDS. Current knowledge on HIV infection and AIDS is extensively discussed in "AIDS, The Unanswered Questions", Science, 260, 1209-1396 (May 1993).

Compound Synthesis


Some compounds of the invention may be synthesized using the diquaternary ammonium salt synthesis method described in U.S. Patent No. 5,256,391.

The following examples illustrate synthesis of the compounds of the invention.
1. **Synthesis of 1,3,5,7-Tetrahydroxyadamantane**

![Chemical Structure](image)

1,3,5,7-Tetrahydroxyadamantane was synthesized by oxidation of adamantane using methyl(trifluoromethyl)dioxirane (References: Oxidation by Methyl(trifluoromethyl)dioxirane. 2. Oxyfunctionalization of Saturated Hydrocarbons, Rossella Mello, Michele Fiorentino, Caterina Fusco, and Ruggero Curci, J. Am. Chem. Soc. 1989, 111, 6749; Oxidation by Methyl(trifluoromethyl)dioxirane. 3. Selective Polyoxyfunctionalization of Adamantane, Rossella Mello, Luigi Cassidei, Michele Fiorentino, Caterina Fusco, and Ruggero Curci, Tetrahedron Lett., 1990, 31, 3067). In present synthesis, a one-pot oxidation procedure was developed. Methyl(trifluoromethyl)dioxirane was generated in situ from 1,1,1-trifluoro-2-propanone (CF₃COCH₃, hereafter TFP) and buffered (pH 7, NaHCO₃) aqueous potassium peroxomonosulfate (KHSO₅). The commercial product triple salt 2KHSO₅.KHSO₅.K₂SO₄ (OXONE by DuPont) was used as a source of potassium peroxomonosulfate.

Into a 4-neck flask immersed in a cooling bath and equipped with a low temperature condenser (-20°C), an air driven, well sealed mechanical stirrer, a solid addition funnel, and a thermocouple, were added 5.0 grams adamantane (purified by recrystallization from heptane), 150 ml methylene chloride, 200 ml double distilled water, 192 grams sodium bicarbonate (pH 7 buffer), and 300 ml tert-butanol. The mixture was stirred and cooled to 0°C and 200 grams TFP were added. The temperature rose to 10°C. The mixture was stirred and cooled down to -8°C, 200 grams of OXONE were added from the solid addition funnel in the course of 3 hours. There was no rise in temperature during the OXONE addition. The reaction mixture was stirred at
0°C overnight (16 hours). The TFP was recovered by distillation by heating the pot to 40°C and condensing the TFP in a receiver immersed in dry ice/acetone. The remainder paste-like mixture was filtered by suction with ease, and a clear colorless solution was obtained. The solution was rotavapped to dryness. The crude product by GC analysis contained 95% polyhydroxyadamantane products of which 5% was 1,3,5-tri hydroxyadamantane and 95% was 1,3,5,7-tetrahydroxyadamantane. Pure 1,3,5,7-

tetrahydroxyadamantane was obtained by recrystallizing the crude product from ethanol/methylene chloride. Calculated for C_{10}H_{16}O_4: C:59.98; H:8.06; O:31.96. Found: C:59.75; H:8.23; O:32.02.

2. Synthesis of 1,3-Dihydroxy-5,7-Dimethyladamantane

1,3-Dihydroxy-5,7-dimethyladamantane was synthesized in a similar manner as described for 1,3,5,7-tetrahydro-
adamantane. Into a 4-neck flask immersed in a cooling bath and equipped with a low-temperature condenser (-20°C), an air-driven, well-sealed mechanical stirrer, a solid addition funnel, and a thermocouple, there were charged 4.5 grams, 1,3-dimethyladamantane (Aldrich, 99%+), 100 ml methylene chloride, 96 grams sodium bicarbonate, 100 ml double distilled water. Upon stirring and cooling the mixture to 0°C, 100 grams TFP were added and the temperature of the mixture went to 10°C. After the mixture was cooled down again to 0°C, 100 grams OXONE were added in the course of an hour. The reaction mixture was stirred at -5°C for additional 20 hours (overnight). The TFP was recovered by distilling the reaction mixture at a pot temperature of 50°C into a receiver immersed in dry
ice/acetone. The remainder mixture was filtered by suction over Celite as a filter aid. The filtrate was yellow and contained two phases (aqueous and organic). It was rotavapped to dryness. The dry solid was extracted with ethanol and filtered. Crude product was obtained by evaporating off the ethanol which contained more than 95% 1,3-dihydroxy-5,7-dimethylandamantane. The brownish crude product was purified by crystallization from ethanol/methylene chloride mixture to a GC pure product with a molecular weight of 196 gram/mole (by GC-MS). Calculated for C_{20}H_{20}O: 196.28 gram/mole.

3. Synthesis of N-3-Diamantyl-N,N,N',N'-pentamethyl-1,3-Propane Bis-Quaternary Ammonium Diodide

Starting Materials:

\[
\text{H}_2\text{C-CH}_2-\text{CH}_2-\text{NH}_2, \text{ N, N-Dimethylpropylenediamine}, 100%: 51.1 \text{ gm (0.5 mole) 3-Diamantanone}, 97%: 101.2 \text{ gm (0.5 mole)}. \\
\text{Solvent: Ethanol; 300 ml.}
\]

Catalyst for Hydrogenation: Pd (5 wt. %) on activated carbon, 16.0 gm.

The reactants were mixed in a 600 ml Parr reactor. The reactor was sealed and purged with nitrogen gas, then filled with H₂ for reductive amination. The H₂ pressure in the reactor was maintained at 3550 kPa (500 psig) and H₂ was continuously fed to the Parr reactor from a reservoir bomb. The reaction was carried out at 75°C for 72 hours at which time no more H₂ was taken up. The product (formula 3A) was isolated in 100% yield (143.7 gm). The product
(formula 3A) was methylated and 132 gm of product (formula 3B) was obtained in 84% yield based upon starting materials. The product (formula 3B) was quaternized with 61.9 gm CH₃I at 45°C or lower by adding the CH₃I slowly to obtain a product having formula 3C in quantitative yield. The product formula 3C was then subjected to further quaternization in DMF with 93 gm additional CH₃I in a 600 ml Parr reactor at 75°C for 72 hours. The reactor was cooled down to ambient temperature and opened. The solid crystalline product was first washed with DMF, then with hot ethanol until the washer was clear (about 5 liters). The washed product was white and dried at 75°C/30 mm Hg to 240.2 gm (82% yield based upon starting materials). The initial DMF washing was rotavapped and the solid product was again washed with ethanol to give an additional 4.5 gm of the product formula 3D. The product of formula 3D was then recrystallized in boiling water and white glistening crystals were obtained from water at room temperature.

Elemental analysis of the product formula 3D:
Calculated for C₂₂H₄₈N₂I₂: C: 45.06; H: 6.88; N: 4.78; I: 43.29.
Found C: 44.99; H: 6.95; N: 4.72; I: 43.23.
4. Synthesis Of N-2-Adamantyl-N,N,N’N’N’-Pentamethyl-1,2-Ethane Diquaternary Ammonium Diiodide

5 Synthesis (3) was repeated using the following starting materials:

CH₃
CH₃-N-CH₂-CH₂-NH₂  N,N,-Dimethylethylenediamine, 95%
111.4 gm (1.2 moles).

10 2-adamantanone, 99%: 151.7gm (1.0 mole).
Solvent: cyclohexane: 300 ml
Temperature: The pot temperature was kept at about 80°C and water was azeotroped out at 69°C.
### Products:

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>\textsuperscript{13}CNMR</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure1" /></td>
<td>100</td>
<td>180.7, 60.9, 48.3, 46.0, 43.9, 39.3, 38.5, 36.7, 33.4, 28.0</td>
<td>----</td>
</tr>
<tr>
<td><img src="image2" alt="Structure2" /></td>
<td>100</td>
<td>62.3, 60.9, 48.3, 45.7, 38.2, 37.8, 32.3, 31.5, 28.0</td>
<td>----</td>
</tr>
<tr>
<td><img src="image3" alt="Structure3" /></td>
<td>90</td>
<td>67.7, 56.6, 52.4, 46.4, 39.8, 38.2, 37.7, 31.7, 30.0, 27.8, 27.6</td>
<td>----</td>
</tr>
<tr>
<td><img src="image4" alt="Structure4" /></td>
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<td>69.3, 63.3, 54.4, 48.5, 41.5, 40.2, 39.7, 33.5, 31.9, 29.2 (2 types)</td>
<td>Calculated for C_{n}H_{2n}N_{2}I: C: 50.79; H: 8.26; N: 7.40; I: 33.5</td>
</tr>
<tr>
<td><img src="image5" alt="Structure5" /></td>
<td>90</td>
<td>83.0, 61.4, 59.7, 57.4, 54.5, 42.8, 39.9, 34.2, 31.7, 29.9, 28.7</td>
<td>Calculated for C_{n}H_{2n}N_{2}I: C: 39.25; H: 6.59; N: 5.38; I: 48.79</td>
</tr>
</tbody>
</table>

*Yield based on 2-adamantanone*

For the synthesis of the compound when \( n = 3 \), the starting materials are:

- CH\(_3\)N-CH\(_2\)-CH\(_2\)-CH\(_2\)-NH\(_2\) N,N-Dimethylethylenediamine, 95% 122.6 gm (1.2 moles).
- 2-adamantanone, 99%: 151.7gm (1.0 mole).

Solvent: cyclohexane: 300 ml

Temperature: The pot temperature was kept at about 80°C and water was azoetrapped out at 69°C.
### Product:

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield, %</th>
<th>$^{13}$C-NMR</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
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<td>179.9, 581.47.9, 45.7, 43.9, 39.3, 38.4, 36.6, 33.0, 29.5, 27.9</td>
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</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>97</td>
<td>62.3, 58.8, 46.0</td>
<td>----</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>74</td>
<td>67.3, 58.7, 52.1</td>
<td>----</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>69</td>
<td>71.0, 68.8, 57.1</td>
<td>----</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>70</td>
<td>83.1, 66.6, 64.4, 57.4, 54.6, 43.4, 40.6, 34.7, 32.2, 30.5, 29.2, 21.0</td>
<td>Calculated for C$<em>{18}$H$</em>{28}$N$_2$I$_2$; C:40.46; H: 6.79; N: 5.24; I: 47</td>
</tr>
<tr>
<td><img src="image6" alt="Structure 6" /></td>
<td>70</td>
<td>83.1, 66.6, 64.4, 57.4, 54.6, 43.4, 40.6, 34.7, 32.2, 30.5, 29.2, 21.0</td>
<td>Found: C:40.09; H: 6.89; N: 5.19; I: 48.23</td>
</tr>
</tbody>
</table>

*Yield based on 2-adamantanone.

5. **Synthesis of N-2-Adamantyl Glycine**

![Structure 7](image7)

This compound was synthesized by reductive amination of 2-adamantanone with glycine. A 600 ml stainless steel Parr
reactor, equipped with a stirrer, two inlets, one with a tubing reaching nearly to the bottom of the reactor, and an outlet was used. Into the open reactor there were charged 100 grams of glycine (Aldrich. 99+%), 206.7 grams of 2-adamantanone (Aldrich, 99%), 10 grams of palladium (5%) on charcoal, and 300 grams of glacial acetic acid. The reactor was cooled and assembled in the hood with nitrogen and hydrogen sources. The reaction mixture was bubbled with dry nitrogen, to replace the air in the reaction mixture and in the reactor, through the inlet with a tubing reaching nearly to the bottom of the reactor. The nitrogen was turned off and the reactor was pressurized with hydrogen through the other inlet. Under a hydrogen pressure of 6100 kPa (725 psig), the reaction mixture was heated to 100°C and stirred at this temperature for 5 days. Hydrogen was refilled whenever it was necessary. After cooling down to room temperature, the excess hydrogen was vented from the reactor and the reactor was opened. The mixture was filtered by suction to remove the solid Pd/C catalyst. The filtrate was rotavapped to remove the acetic acid and water. The crude product was washed with ether and recrystallized from a dilute aqueous solution. A pure product was obtained after two recrystallizations. Elemental analysis: Calculated for C₁₉H₂₄NO₂: C:68.87; H:9.15; N:6.69. Found: C:68.85; H:9.12; N:6.75.

6. Synthesis of 3-Diamantane

3-Diamantane can be synthesized from diamantane by the method described by Courtney et. al., J. Chem. Soc. Perkin
Trans. I 1972, 2691-6 employing concentrated sulfuric acid at 75°C for four hours to convert diamantane to 3-diamantanone at 54% yield. Gund et al., J. Org. Chem. 1974, 39(20), 2987-94, used the same procedure to obtain the ketone from diamantane. See also, Gund et al., Tetrahedron Letter 1970, 4875-8. Janku et al., Z. Chem. 1981, 21, 67-68 described a similar procedure giving 86% yield of 3-diamantanone. We have used a modification of the method of Janku et al. by reacting diamantane with concentrated sulfuric acid (about 5 ml conc. H₂SO₄/g diamantane) at 80°C for 48-96 hours. The time required depends on the agitation and the mixing of the subliming diamantane with the acid solution. The progress of the reaction can be monitored by taking small aliquots from the reaction mixture and performing standard aqueous work-up procedure to give solutions analyzed by gas chromatography method. At the end of the reaction, the solution is cooled and any small amount of unreacted diamantane solid removed by filtration. The resulting acid solution is poured into ice. The crude product was collected by filtration, washed thoroughly with water, and dried. The slight discoloration of the crude product can be removed by dissolving the product in hot hexanes and filtering through a solid absorbant such as silica gel or alumina. The crude product, often consisting of over 97% 3-diamantanone, can be further purified by standard techniques to give 3-diamantanone with purities of 99.5 -99.9% based on gas chromatography analysis. One method involves recrystallization using ethyl acetate or hexanes. Another involves liquid chromatography on silica gel using a gradient of 0-10% acetone in hexanes as the eluent. The purified product tested has a melting point of 248.8-250.8°C. It shows the expected proton and carbon 13 NMR spectra. GC analysis showed less than 0.7% impurities.

The yields of 3-diamantanone range from 83-90% using our
method for reactions employing about 30 to 450 g of diamantane.

7. Synthesis of 2,4-Adamantanedione

2,4-Adamantanedione has been synthesized by oxidation of adamantanone with CrO₃, and isolating it from the resulting complex mixture at a low yield (Gilbert, Synthetic Communication 1985, 15(1), 53-56). Alternatively, adamantane-2,4-dione was made by a three-step procedure which requires a chromatographic separation at one of the steps (Faulkner et al., J. Chem. Soc. (C), 1971, 3606-10; Henkel and Spector, J. Org. Chem. 1983, 48, 3657-61). An improved synthesis of this dione, which does not require a chromatographic separation, is described in U.S. Patent No. 5,298,666.

8. Synthesis of 4(e)-Hydroxy-2-Adamantanone Ethylene Glycol Ketal

This compound was synthesized using the procedure described by Henkel and Spector, J. Org. Chem. 1983, 48, 3657-61. It can also be made using the improved synthesis of its hydroxy precursor described in U.S. Patent No. 5,298,666.
The following diamondoid compounds were dissolved in ethanol at a concentration of 20mg/ml:

**Compound**

1. 1,3,5,7-tetrahydroxyadamantane
2. 1,3-dihydroxy-5,7-dimethyladamantane
3. N-3-diamantyl-N,N,N',N',N'-pentamethy propane-1,3-bis ammonium diiodide
4. N-2-adamantyl-N,N,N',N'-pentamethyl ethane-1,2- bis ammonium diiodide
5. N-2-adamantyl glycine
6. 3-diamantanone
7. 2,4-adamantanedione
8. 4(e)-hydroxy-2-adamantanone ethylene glycol ketal

**Cell Line**

The MT-2 cell line, a human T-cell leukemia line derived from isolated cord blood lymphocytes cocultured with cells from patients with adult T-cell leukemia, was obtained from AIDS Research and Reference Reagent Programme of the NIAID, NIH (cat. no. 237, NIH, Bethesda, MD). The MT-2 cell line can be successfully used as targets for HIV-1 infection and requires only 4 to 5 days for complete cytopathic effect (CPE). (Montefiori et al., J. Clin. Microbiol 1988, 26, 231-235; Pauwels et al., J. Virol. Meth. 1988, 20, 309-321; Harada et al., Science 1985, 229, 563-6)

The MT-2 cell line was grown and maintained in RPMI 1640 containing 10% fetal calf serum and antibiotics.

**Viruses**

MN/H9 (HIV-1<sub>MN</sub>) (cat. no. 317) was obtained from the AIDS repository.

The AZT resistant strain (AZTR) of HIV-1 (cat. no. 629) which was isolated from an AIDS patient and developed by Douglas Richman was also obtained from the AIDS repository. (Larder et al., Science, 1989, 243, 1731-1734)
VP6 was a primary HIV isolate obtained by culturing PBMC from a patient with full blown AIDS and kaposi sarcoma, with normal phytohemagglutinin (PHA) stimulated PBMC. Virus-infected cells were grown in RPMI 1640 medium, supplemented with 10% fetal bovine serum and 10% interleukin - 2. Cell-free supernatant fluid was collected when the cultures showed peak infectivity titer and was used as the virus stock. AZTR and VP6 stocks were grown in MT-2 cells. MN was grown in H9 cells. The cell free virus stocks were prepared as per the standard (HIV Research Protocol). The virus stocks were titrated by tissue culture infective dose (50%) TCID₅₀ by inoculating tissue culture and determining observable effects in 50% of the cultures per Reed and Muench, Amer. J. Hyg., 1938, 27, 493-7.

The invention will now be more particularly described with reference to the Examples and the accompanying drawings in which:

Figure 1 is a protocol for an MTT reduction antiviral assay;

Figure 2A-F are photographs illustrating syncytia inhibition against HIV-1/MN virus strain;

Figure 3A-F are photographs illustrating syncytia inhibition against HIV-1/AZTR and VP6 virus strains;

Figure 4 shows graphical representations of inhibition of HIV-1/MN induced CPE by the compounds of the invention.

EXAMPLE 1

Cytotoxicity Assay

An effective anti-viral drug must be non-toxic to cells. Any antiviral assays must first confirm the testing candidate is not cytotoxic to the cells used in the assay. Because viruses use cellular machinery for replication, cytotoxic compounds would inhibit viruses by definition. The microliter cytotoxicity assay used was based on the ability of living cells to reduce the tetrazolium salt MTT
(3[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) and form a blue product (Tada, H, et al., J. Immuno. Meth. 1986 93, 157-165; Carmichael et al., Cancer Research 1987, 47, 936). Precisely, when the MT-2 cells were in log phase and 2x10^4 cells were distributed in each well along with separate 100μl aliquots of diluted test compounds. The test compounds were soluble in ethyl alcohol (EtOH). Ethanol and medium were incubated in some wells with the cells as an ethanol control. A cell control was also included (wells containing only cells and medium). The plates were incubated for 5 days at 37°C in 5% CO₂ and humidified conditions. Cell viability was determined in each well by the MTT assay. The details of the assay are summarized in Fig. 1. The OD₅₇₀ (optical density at 570nm) of cells without test compound was taken as 0% killing and was compared to the OD₅₇₀ of cells with test compound. The toxicity profile for different compounds was then scored. The results are shown in Table 1. In the MTT dye reduction assay toxicity was indicated as yellow in the wells, with blue color indicating the compound was non-toxic.

| TABLE 1 |
|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Compound | Solubility | Toxicity (µg/ml) |
|          | H₂O | EtOH | 500 | 50 | 5 | .5 |
| 1        | + | + | - | - | - | - |
| 2        | - | + | + | - | - | - |
| 3        | + | + | + | - | - | - |
| 4        | + | + | - | - | - | - |
| 5        | + | + | - | - | - | - |
| 6        | + | + | + | - | - | - |
| 7        | + | + | - | - | - | - |
| 8        | + | + | + | - | - | - |

- = non-toxic
The toxicity of the compounds was tested at concentrations up to 500 μg/ml. The results in Table 1 show that the compounds were non-toxic at most therapeutically useful concentrations.

**EXAMPLE 2**

**Anti-HIV Assay**

Stock solutions of the different test compounds were appropriately diluted to give final concentration of 2.5, 5, 10 and 20 μg/ml in RPMI medium when 100μl of each dilution was added to three replicate wells in 96-well flatbottomed microliter plates. MT-2 cells were inoculated with 100 TCID 50 of HIV-1/MN, the AZT resistant isolate or the VP6 isolate in Ti-25 flasks and incubated for two hours at 37°C. The cells were then washed to remove any remaining free virus, and 2x10⁴ cells were distributed to each of the wells. In cell control only, uninfected cells were distributed. Virus control wells had only infected cells and medium. The plates were incubated at 37°C for 5 days. HIV-1 induced syncytia were observed after 48 hours.

Pictures were taken, shown in Fig 2 and Fig 3. After day 5, when maximum CPE was observed in virus control wells, the MTT assay was performed and percent protection was calculated for each drug, applying the following formula:

\[
\frac{(OD_{t})_{HIV} - (OD_{t})_{HIV}}{(OD_{c})_{mock} - (OD_{c})_{HIV}} \quad \text{(expressed in %)}
\]

in which (ODₜ)HIV is the optical density measured in HIV-infected cells treated with a given concentration of the test compound; (ODₜ)HIV is the optical density measured for the control untreated HIV-infected cells. (ODₜ)mock is the optical density measured for the control untreated mock infected cells. All O.D. values were determined at 570 nm. For pretreatment experiments, cells were incubated with test compounds for 1 hour at 37°C prior to infection with the virus. After the adsorption of virus, these cells were
washed, the wells replenished with medium containing test compound. The remaining part of the assay was continued as above. Pictures were taken on day 5 (See Fig. 2). The percent protection from these tests was plotted and is depicted in Fig. 4.

**EXAMPLE 3**

**Virus Neutralization Assay**

50μl of cell free virus (100 TCID50) were mixed with 50μl of different concentrations of the test compounds. Virus-compound mixtures were incubated at 37°C for 1 hour, then added to the wells of a 96-well flat-bottomed microtiter plate containing 6x10⁴ MT-2 cells/well. The plates were incubated at 37°C in 5% CO₂ humidified atmosphere for 5 days. MTT reduction assay was performed on day 5. The neutralization pattern was assessed and the results summarized in Table 2.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Post-Infection</th>
<th>Neutralization</th>
<th>Pre-Infection</th>
<th>AZTR Post-Infection</th>
<th>VP6 Post-Infection</th>
<th>AZTR Pre-Infection</th>
<th>VP6 Pre-Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (ND)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>--</td>
<td>--</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**+++ = greatest neutralization**  
**--- = no neutralization**  
**ND = not done**
A rating of ++++ or +++ indicates significant and reproducible inhibition of cytopathic effect; + indicates noticeable but minimal protection; --- or -- means no protective effect was observed. A rating of - indicates no protection was observed but some changes in the cell culture occurred. Because assays in different columns were rated and compared with control for that column, ratings under different columns should not be compared quantitatively. Since the clinical isolates AZTR and VP6 do not induce as severe a cytopathic effect as HIV-1MN does, it is unlikely that any compounds will be rated higher than ++ against the clinical isolates.

As measured by the assays, compounds 1, 2, 3 and 6 were found to be effective in both pre-infection and post-infection assays against the HIV-1MN strain. Compounds 1, 2, 3, 6, 7 and 8 were effective in pre-infection and neutralization assays and compounds 1, 2, 3, 5 and 6 were effective in post-infection assays.

Compound 6 was found to completely inhibit HIV-1MN induced syncytia at a very low concentration (10μg/ml; shown in Figure 2). Compound 7 was found to substantially eliminate syncytia formation. Furthermore, compound 6 was found to be effective in both pre-treatment and in post-infection while compound 7 inhibited viral cytopathic effect in pretreatment of the MN virus strain.

Importantly, compound 6 inhibited virus replication with AZT resistant strains and VP6 clinical isolates as well in both pre- and post-infection assays, while compound 7 inhibited CPE of HIV in pre-infection assays on both AZT resistant and VP6 clinical isolates.

The percent protection by different compounds which inhibited CPE is illustrated in Figure 4. It is clear that some of the derivatives inhibited HIV-1 induced CPE by up to 80%.

We have shown that diamondoid derivatives inhibit HIV-1 induced CPE in living cells as well as syncytia at significant levels. For compound 7, pretreatment is more
effective than post-infection treatment. While not wishing
to be bound by any one theory, this suggests that compound
7 may act early in the viral life cycle to inhibit viral
entry into cells inhibiting initiation of infection or
other steps. Compound 6 is active in both pre- and post-
infecetion and in neutralization assays, suggesting that it
is acting in the later stages of the viral life cycle. No
compound currently approved for use in HIV patients works
at the late stages of the virus life cycle. Furthermore,
compounds 6 and 7 were shown to inhibit clinical isolates
and AZT resistant isolates. It is also noted that
compounds 6, 7 and 8 are diamondoid ketones and
derivatives, for which no known pharmacological activity
has been reported. Compounds 3, 4 and 5 are derived from
ketones as described in the synthesis above. Because some
related compounds have not shown activity against HIV-1 in
the same assays, it is concluded that effective compounds
derive their activity from a particular arrangement of
polar functional groups on the diamondoid framework.

Other compounds tested were \( N-(2\text{-adamantyl})-N,N,N',N'\)-pentamethyl-propane-1,3-bis ammonium diodide, adamantane-
2,6-dione, 5-hydroxy-2-adamantanone, diamantane-3,5-dione
and 2-adamantanone. These compounds were ineffective under
the rigorous testing conditions used in these examples,
e.g., high virus load. It was therefore concluded that
under these rigorous conditions when the compound of
formula I has more than one polar group, a first polar
group is separated from the closest second polar group by
no more than two carbon atoms of the diamondoid compound,
counted by the shortest route. With compounds of formula
II, ketones with a 1,3 relationship were ineffective under
the rigorous testing conditions used in these examples.
CLAIMS:

1. A pharmaceutical composition comprising a compound of formula I, formula II or combinations thereof and a pharmaceutically acceptable carrier or diluent:

\[
\text{formula I}
\]

wherein Y is a bond, CH₂, oxygen, sulfur, sulfoxide, sulfone or NH; R₁, R₄, R₅ and R₁₀ are individually hydrogen, hydroxyl, lower alkyl of 1 to 8 carbon atoms, OZ where Z is lower alkyl of 1 to 8 carbons, COQ where Q is hydrogen or lower alkyl of 1 to 8 carbons, or OSO₂H; R₂, R₃, R₆, R₇, R₈, R₉, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ are individually hydrogen, hydroxyl, lower alkyl of 1 to 8 carbons, double-bonded oxygen, COQ where Q is hydrogen or lower alkyl of 1 to 8 carbons; OQ’ where Q’ is hydrogen, lower alkyl of 1 to 8 carbons or aryl; OSO₂H, D

\[
(\text{CH}_₂)_n
\]

where n is 2 or 3 and D is oxygen or sulfur; COOQ where Q is hydrogen or lower alkyl of 1 to 8 carbons, (OZ)₁; where Z is lower alkyl of 1 to 8 carbons; where Z’ is hydrogen,

\[
\text{NH}_₂, \text{OH}, -\text{NH-C-NH}_₂ \text{ or } -\text{NH-C-NH}_₂; \text{NHQ“ where Q” is lower alkyl of 1 to 5 carbons; an amino acid, SH, or a moiety of formula A}
\]
formula A

wherein $R_a$ is hydrogen or lower alkyl of 1 to 8 carbons; $R_b$ is lower alkyl of 1 to 8 carbons; $R_c$ is hydrogen or lower alkyl of 1 to 8 carbons; $X^-$ is a counterion; and $R_{1-16}$ are not all hydrogen;

formula II

wherein $Y$ is a bond, $\text{CH}_2$, oxygen, sulfur, sulfoxide, sulfone or NH; $R_{17}$, $R_{18}$, $R_{21}$, $R_{24}$, $R_{25}$, $R_{28}$, $R_{31}$ and $R_{32}$ are individually hydrogen, hydroxyl, lower alkyl of 1 to 8 carbons, OZ where Z is lower alkyl of 1 to 8 carbons, COQ where Q is hydrogen or lower alkyl of 1 to 8 carbons, $\text{OSO}_2\text{H}$, $\text{NH}_2$, $\text{NHR}'$, $\text{NR}'\text{R}''$, $\text{NR}'\text{R}''\text{R}'''$,

$-\text{O-}C-R'$ where $R'$, $R''$ and $R'''$ are individually lower alkyl of 1 to 8 carbons, SH, aryl, furyl or pyridyl;

$R_{19}$, $R_{20}$, $R_{22}$, $R_{23}$, $R_{26}$, $R_{27}$, $R_{29}$, $R_{30}$, $R_{33}$, $R_{34}$, $R_{35}$ and $R_{36}$ are individually hydrogen, hydroxyl, double-bonded oxygen, COQ where Q is hydrogen or lower alkyl of 1 to 8 carbons, OCOQ' where Q' is hydrogen, lower alkyl of 1 to 8 carbons or aryl; $\text{OSO}_2\text{H}$, $-\text{D}$

$-\text{D}$

$(\text{CH}_2)_n$
COOQ where Q is hydrogen or lower alkyl of 1 to 8 carbons, (OZ), where Z is lower alkyl with 1 to 8 carbons, =NZ'

where Z' is hydrogen, NH₂, CH, -NH-C-NH₂ or -NH-C-NH₂;
NH₂, NHR', NR'R'' where R' and R'' are individually lower alkyl of 1 to 8 carbons; SH, an amino acid or a moiety having formula B or formula C

\[
\begin{align*}
\text{or} & \\
\text{N} & \quad \text{or} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \quad \text{(X')} \\
\text{R} & \quad \text{R} \quad \text{R} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]

formula B \quad formula C

wherein R₃ is hydrogen or lower alkyl of 1 to 8 carbons; 
R₄ is \((\text{CH}_₂)_n\text{N(CH}_₃)_2\text{, (X')}\) where n = 2 or 3 and X' is a counterion; or lower alkyl of 1 to 8 carbons, R₅ is 
lower alkyl of 1 to 8 carbons; R₁₇-₃₆ are not all hydrogen; and wherein all substituents in formula I and

formula II contribute to a stable molecule.

2. The composition of claim 1 wherein the compound is selected from diamondoid alcohols, diamondoid polyols, diamondoid amino acids, diamondoid quaternary ammonium salts, diamondoid ketones and their carbonyl derivatives and combinations thereof.

3. The composition of claim 1 wherein the compound of formula I is selected from 1,3,5,7-adamantane tetraol; 1,3-dihydroxy-5,7-dimethyladamantane; N-2-adamantyl glycine; 2,4-adamantanedione; 4(e)-hydroxy-2-
adamanatanone ethylene glycol ketal and combinations thereof.
4. The composition of claim 1 wherein the compound of formula II is selected from N-3-diamantyl-N,N,N',N',N'-pentamethyl-propane-1,3-bis ammonium diiodide and 3-diamantanone.

5. The composition of claim 1 wherein the compound is selected from 2,4-adamantanedione, 3-diamantanone and 4(e)-hydroxy-2-adamantanone ethylene glycol ketal.

6. The composition of claim 1 wherein the compound is 2,4-adamantanedione.

7. The composition of claim 1 wherein the compound is 3-diamantanone.

8. The composition of claim 1 wherein the compound is 4(e)-hydroxy-2-adamantanone ethylene glycol ketal.

9. Use of the composition of any one of the preceding claims in the inhibition of a virus.

10. Use of claim 9 wherein the virus is a retrovirus.

11. Use of claim 10 wherein the retrovirus is HIV-1.
ADD MT-2 CELLS TO WELLS

ADD DRUGS AND HIV VIRUS TO CELLS

INCUBATE AT 37° FOR 5 DAYS

ADD MTT TO CELLS

INCUBATE AT 37° FOR 5 HOURS

ADD 10% SDS/.01 M HCl

READ OD AT 570nm

FIG. 1
### A. CLASSIFICATION OF SUBJECT MATTER

**IPC(S):** Please See Extra Sheet.

**US CL:** Please See Extra Sheet.

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)

- U.S.: 514/461, 561, 642, 661, 662, 691, 729; 549/341; 562/498, 499; 564/281, 458, 459; 568/368, 373, 817, 818

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

CAS online -- CA and Registry Files

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X, P</td>
<td>US, A, 5,256,391 (Chen et al.) 26 October 1993, see examples.</td>
<td>1, 2, 4</td>
</tr>
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<td>X</td>
<td>US, A, 5,194,538 (Puskas et al.) 16 March 1993, see bottom of column 3.</td>
<td>1-3</td>
</tr>
<tr>
<td>X</td>
<td>US, A, 5,019,660 (Chapman et al.) 28 May 1991, see examples.</td>
<td>1-7</td>
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<tr>
<td>Y</td>
<td>US, A, 4,622,430 (Dekker et al.) 11 November 1986, see columns 1 and 2.</td>
<td>1, 2, 9-11</td>
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<tr>
<td>X</td>
<td>US, A, 3,356,741 (Schneider) 05 December 1967, see examples.</td>
<td>1-3, 9-11</td>
</tr>
<tr>
<td>X</td>
<td>US, A, 4,956,481 (Gillaspey et al.) 11 September 1990, see Table II and example XXIII.</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

X Further documents are listed in the continuation of Box C. See patent family annex.

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document published on or after the international filing date
- "L" document which may throw doubt 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
- "S" member of the same patent family

Date of the actual completion of the international search: 12 SEPTEMBER 1994

Date of mailing of the international search report: SEP 22 1994

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer: PETER G. O'SULLIVAN
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)
### INTERNATIONAL SEARCH REPORT

**International application No.**
PCT/US94/06126

#### C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US, A, 3,257,456 (Smith) 21 June 1966, see entire document.</td>
<td>1, 2, 9-11</td>
</tr>
<tr>
<td>Y</td>
<td>US, A, 3,450,761 (Schneider) 17 June 1969, see entire document.</td>
<td>1, 2, 9-11</td>
</tr>
<tr>
<td>Y</td>
<td>DE, A, 3,921,062 (Lange et al.) 03 January 1991, see lines 20-25 of page 3.</td>
<td>9-11</td>
</tr>
<tr>
<td>X</td>
<td>R.C. Fort, Jr., &quot;Adamantane, the Chemistry of Diamond Molecules&quot;, published 1976 by Marcel Dekker (New York), see pages 327-357.</td>
<td>1, 2, 9-11</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet)(July 1992)
INTERNATIONAL SEARCH REPORT

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

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

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

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:

Please See Extra Sheet.

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 searched 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.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*
A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):
A61K 31/045, 31/12, 31/13, 31/14, 31/95, 31/335; C07C 35/37, 35/44, 49/42, 49/453, 61/12, 211/38, 211/62; C07D 317/72

A. CLASSIFICATION OF SUBJECT MATTER:
US CL.:
514/461, 561, 642, 661, 662, 691, 729; 549/341; 562/498, 499; 564/281, 458, 459; 568/368, 373, 817, 818

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:
I. Claims 1-3 and 9-11, drawn to hydroxy substituted adamantane compositions and methods.
II. Claims 1, 2, 4, and 9-11, drawn to diamantyl substituted bis-ammonium propane compositions and use.
III. Claims 1-3 and 9-11, drawn to diamantyl glycine compositions and methods.
IV. Claims 1, 2, 4, 5, 7, and 9-11, drawn to diamantanone compositions.
V. Claims 1, 2, 3, 5, 6, and 9-11, drawn to adamantanedione compositions.
VI. Claims 1, 3, 5, and 8-11, drawn to hydroxyadamantane ethylene glycol ketal compositions.

Inventions I-VI lack unity of invention under PCT Rules 13.1 and 13.2 in that they lack a single inventive concept. PCT Administrative Instructions, Annex B, (f,f).