Synthetic HIV Protease Gene and Method for Its Expression

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Filed 02 Mar 93

Serial No. 08/024,916 (CIP of U.S. Patent 5,252,477)

Inhibition of the HIV protease enzyme is currently an important component of combination therapies for HIV infection and AIDS. This patent application discloses a DNA construct for biologically active recombinant HIV–1 protease, as well as a method for its production and purification. The recombinant enzyme can be used to design HIV–1 protease inhibitors and to test their effectiveness against HIV–1. This technology is described further in Louis, J.M., et al., *Biochem Biophys Res Comm* 159(1): 87–94 (1989). Foreign intellectual property rights are available in Australia, Canada, Israel, and Japan. (Portfolio: Infectious Diseases—Reagents)

Transframe Peptide Inhibitor of Viral Protease

JL Medabalimi (NIDDK)

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Serial No. 08/539,432

The inhibition of protease is an increasingly important approach in the control of pathogenic organisms, including retroviruses such as the human immunodeficiency virus (HIV). The present invention embodies small, water-soluble peptides isolated from a native retroviral inhibitory sequence that block maturation of HIV protease and also inhibit the mature enzyme. The peptides may be used in the treatment of HIV-infected cells, in the preparation of HIV vaccine formulations, in the generation of clinically relevant anti-HIV antibodies and anti-idiotypic antibodies, and as components of a screening assay or kit used to identify other similarly acting HIV protease inhibitors. The invention encompasses the inhibitory peptides, pharmaceutical compositions containing the peptides, methods of using the peptides in the treatment and prevention of HIV-induced pathogenesis, a kit and methods for screening test compounds (peptide or non-peptide) for use as HIV protease inhibitors, and antibodies and anti-idiotype antibodies to HIV protease. (Portfolio: Infectious Diseases—Therapeutics, anti-virals, AIDS; Infectious Diseases—Vaccines, viral, AIDS; Infectious Diseases—Reagents)

2,5-Diamino-3,4-Disubstituted-1,6-Diphenylhexane Isosteres Comprising Benzamide, Sulfonamide and Anthranilimide Subunits and Methods of Using Same

RS Randad, JW Erickson (NCI)
Filed 20 Dec 94
Serial No. 08/359,612

This invention concerns retroviral protease inhibitors which are potential drugs for the treatment of HIV infection and AIDS. The compounds of the invention contain novel nonpeptidic and achiral substituents, wherein achiral benzamide, sulfonamide and anthranilamide subunits are introduced onto the 2,5-diamino-3,4-disubstituted-1,6-diphenylhexane isostere core. The compounds are resistant to viral and mamalian protease degradation. The best compounds had a K_i (inhibition constant) of less than 100 pM for HIV protease. CEM cells chronically infected with HIV–1 were used to test the *in vitro* anti-retroviral activity of the compounds. The concentrations needed to inhibit 50% of viral activity were on the order of 5 nM. Therefore, these compounds compare favorably in their anti-retorviral potency to HIV protease inhibitors currently in clinical trials and on the market. These compounds are described in three recent publications: Randad, R.S., et al., *Bioorganic & Medicinal Chemistry Letters*, 5(15): 1707–1712 (1995); Randad, R.S., et al., *Bioorganic & Medicinal Chemistry Letters*, 5(21): 2557–2562 (1995); and Randad, R.S., et al., *Bioorganic & Medicinal Chemistry Letters* (1996, in press). Foreign intellectual property rights are available in PCT member countries. (Portfolio: Infectious Diseases—Therapeutics, anti-virals, AIDS)

Novel Retroviral Agents Containing Anthranilamide, Substituted Benzamide and Other Subunits, and Methods of Using Same

RS Randad, JW Erickson, TN Bhat (NCI)
Filed 22 Nov 95
Serial No. 08/562,013

This invention concerns retroviral protease inhibitors which are potential drugs for the treatment of HIV infection and AIDS. The compounds of the invention are symmetric and asymmetric 2,5-diamino-3,4-disubstituted-1,6-diphenylhexane (DAD) isosteres with achiral, nonpeptidic anthranilimide, substituted benzamide, sulfonamide and other subunits. The DAD isosteres may also include amino acid subunits. The compounds are more resistant to mammalian and viral protease degradation than currently available retroviral protease inhibitors, and therefore, have greater plasma half-life and oral bioavailability. Pharmacokinetic and bioavailability studies are currently being conducted. The best compound has a K_i (inhibition constant) of approximately 3 pM for HIV protease. *In vitro* anti-retroviral activity was tested in CEM cells chronically infected with HIV–1. The concentration required to inhibit 50% of viral activity was on the order of 6 nM. This compound thus compares favorably in its *in vitro* anti-retroviral potency to HIV protease inhibitors currently in clinical trials and on the market. (Portfolio: Infectious Diseases—Therapeutics, anti-virals, AIDS)

Dated: July 30, 1996.

Barbara M. McGarey,

Deputy Director, Office of Technology Transfer.

[FR Doc. 96–20266 Filed 8–7–96; 8:45 am]

BILLING CODE 4140–01–M

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health.

ACTION: Notice.

The inventions listed below are owned by agencies of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for U.S. companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications and issued patents listed below may be obtained by contacting David Sadowski at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804 (telephone: 301/496–7056 ext 288; fax: 301/402–0220). A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Nurse's Hand Protection

B Thornton, A Peterson, M Allen, B Fahey, M Woolery Antill, J Taylor, V Wheeler, P Coleman, S Kedrowski, L Jeanneret (CC)
Filed 15 Aug 95
Serial No. 08/515,499

This invention provides nurses and other health care workers with protection against accidental needle sticks. Specifically, a device has been

created which protects the most susceptible areas on the back and sides of the thumb, forefinger, and the area of the hand there between. This offers the notable advantage of preventing infections from accidental needle sticks. This invention is particularly useful during the risky task of inserting a twisted or kinked needle (such as a Huber needle) into a pot-a-cath. Stage of Development: prototype built. (portfolio: Devices/Instrumentation—Environmental Technology, prevention, apparatus; Devices/Instrumentation—Miscellaneous)

Separation of Polar Compounds by Affinity Countercurrent Chromatography

Y Ma, Y Ito (NHLBI)
Filed 14 Aug 95
Serial No. 08/514,917
Patent Status: U.S. patent application pending, foreign rights available

A new and highly advantageous method of purifying polar organic compounds using affinity countercurrent chromatography, has been created. This invention permits separation of very hydrophilic organic compounds using countercurrent chromatography in which a ligand for the desired analytes is used to enhance the partitioning of polar species into the organic layer of an aqueous-organic solvent mixture. Examples of polar organic compounds which may be recovered using the present invention include: compounds having two or more functional groups on each molecule which are hydroxyl, amino, acid or lower acyl (e.g., catecholamines, carbohydrates, polyalcohols, polyamines, amino acids, peptides, and nucleic acids). Stage of Development: completed and tested. (portfolio: Devices/Instrumentation—Research Tools, devices, chromatographic)

Apparatus and Method for the In-Situ Detection of Areas of Cardiac Electrical Activity

H Bassen, V Krauthamer (FDA)
Filed 11 Aug 95
Serial No. 08/513,713
Patent Status: U.S. patent application pending and foreign rights available

This invention provides new means for diagnosis (e.g., two dimensional mapping) and treatment of electrically-active tissue without the need for surgery. For example, electrical activity of the heart may be mapped *in vivo*, in a minimally invasive manner, without cutting either the chest wall or the heart wall. The invention employs a multifibered endoscope and multiple tissue dyes to map electrical activity. This permits identification and treatment of potentially lethal electrical abnormalities without surgery. In regard to the cardiac diagnosing aspect of this invention alone, over 400,000 people die in the U.S. each year from cardiac electrical rhythm diseases. This invention provides a minimally invasive and less expensive means for diagnosis and treatment of such diseases. (portfolio: Devices/Instrumentation—Diagnostics, devices, invasive; Devices/Instrumentation—Diagnostics, imaging; Devices/Instrumentation—Therapeutics, devices)

Displacement Countercurrent Chromatography

Y Ito (NHLBI)
Serial No. 08/263,924 Filed 21 June 94
U.S. Patent No. 5,449,461 issued 12 Sep 95

A new method of preparative scale pH-zone refining countercurrent chromatography has been invented, which may be operated analogously to displacement chromatography. It has been discovered that use of a retainer base or acid in the stationary phase retains analytes in the column. The analytes may then be eluted using a displacer acid or base in order of increasing or decreasing pKa or hydrophobicity. This invention has many advantages, including: producing a train of highly concentrated rectangular solute peaks with minimum overlap; the retaining and displacing compositions may be switched (i.e., the retaining material may be made the displacing material, and vice versa); eluted material is provided as a salt free acid or base in an organic solvent, which can easily be separated by evaporating the solvent; the displacement mode of this invention may be utilized in a ligand-affinity separation which may cover a broad range of analytes, including nonionizable compounds; allowing the sample to be loaded onto the separation column as a suspension, or as a mixture of compounds that are only partially soluble in the solvent system, and; permitting the separation of greater volumes than with previous methods. (portfolio: Devices/Instrumentation—Research Tools, devices, chromatographic)

Method for In Situ Testing of Integrity of Electrical Stimulator Leads

R Schmukler (FDA)
Filed 21 Jun 94
Serial No. 08/263,312

This invention provides an in situ method for testing the integrity of the insulation of electrical stimulators leads. It allows the electrical stimulator to measure and thereby continually monitor the insulation of its leads. By being able to detect premature degradation of the leads of implanted electrical stimulators, e.g., pacemakers, unexpected failures of the device can be reduced. Replacement of the electrical stimulator leads in the heart is a traumatic process, to be avoided unless necessary. Currently available pacemakers and other implanted electrical stimulators do not allow for accurate monitoring of the lead insulation, so that advance warning of degradation may be obtained. This invention allows for the degradation of the lead insulation to be detected earlier than is now possible, thereby providing warning of potential failure before it becomes critical to the patient. (portfolio: Devices/Instrumentation—Therapeutics, devices, implants)

A Detection Device and Quantification Method for Therapeutic Agents in Blood

E Kohn, L Liotta (NCI)

Serial No. 08/041,438 filed 31 Mar 93

U.S. Patent No. 5,405,782 issued 11 Apr 95

New methods have been invented which provide improved determination of therapeutic agents in blood. A solid phase extraction of a solute from plasma is followed by reverse phase high performance liquid chromatography on a column of irregularly shaped C–18 liquid chromatography on a column of irregularly shaped C–18 modified silica. By comparing the chromatogram produced by this invention with a standard, a precise and accurate quantification of the amount of solute in the blood may be made. This invention also has the advantage of facilitating automation of the extraction and chromatography steps, thereby permitting rapid testing of a plurality of samples. (portfolio: Devices/Instrumentation—Research Tools, devices, chromatographic; Devices/Instrumentation—Research Tools, devices, separation; Cancer—Therapeutics, conventional chemotherapy, antimetabolites)

Dated: July 30, 1996.

Barbara M. McGarey,

Deputy Director, Office of Technology Transfer.

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