US007112565B2

(12) **United States Patent**
Sawai et al.

(10) **Patent No.: US 7,112,565 B2**
(45) **Date of Patent: *Sep. 26, 2006**

(54) **STABILIZED PHARMACEUTICAL COMPOSITION IN LYOPHILIZED FORM**

(75) Inventors: **Seiji Sawai**, Takarazuka (JP); **Akihiro Kasai**, Ikoma (JP); **Kazumi Ohtomo**, Ibaraki (JP)

(73) Assignee: **Astellas Pharma Inc.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 307 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/772,281**

(22) Filed: **Feb. 6, 2004**

(65) **Prior Publication Data**

US 2004/0157769 A1 Aug. 12, 2004

Related U.S. Application Data

(62) Division of application No. 09/786,125, filed as application No. PCT/JP00/04381 on Jun. 29, 2000, now Pat. No. 6,774,104.

(30) **Foreign Application Priority Data**

Jul. 1, 1999 (JP) 11/187713

(51) **Int. Cl.**
A61K 38/00 (2006.01)
A61K 38/12 (2006.01)

(52) **U.S. Cl.** **514/9**; 514/2; 514/11; 514/15; 530/317; 530/323

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,376,634	A	12/1994	Iwamoto et al.	
5,569,646	A	10/1996	Ohki et al.	
5,942,510	A	8/1999	Floyd et al.	
6,207,434	B1	3/2001	Ueda et al.	
6,399,567	B1	6/2002	Kanasaki et al.	
6,774,104	B1 *	8/2004	Sawai et al.	514/9

FOREIGN PATENT DOCUMENTS

JP	3-193735	8/1991
JP	3-240727	10/1991
JP	6-51641	7/1994
JP	9-301997	11/1997
JP	10-507174	7/1998
WO	WO 96/11210	4/1996
WO	WO 97/39763	10/1997
WO	WO 00/51564	9/2000
WO	WO 00/51567	9/2000

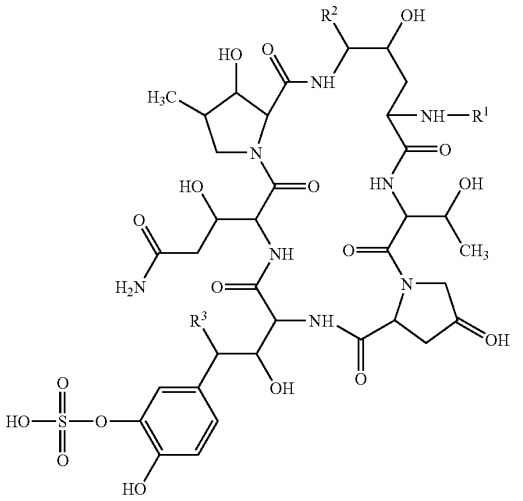
* cited by examiner

Primary Examiner—B. Dell Chism
(74) *Attorney, Agent, or Firm*—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

(57) **ABSTRACT**

A stabilized pharmaceutical composition in lyophilized form comprising: a cyclic polypeptide compound represented by the general formula (I):

(I)



wherein R^1 is a hydrogen atom or an acyl group and R^2 and R^3 are, the same or different, a hydrogen atom or a hydroxyl group, or a salt thereof and the stabilizer.

23 Claims, No Drawings

STABILIZED PHARMACEUTICAL COMPOSITION IN LYOPHILIZED FORM

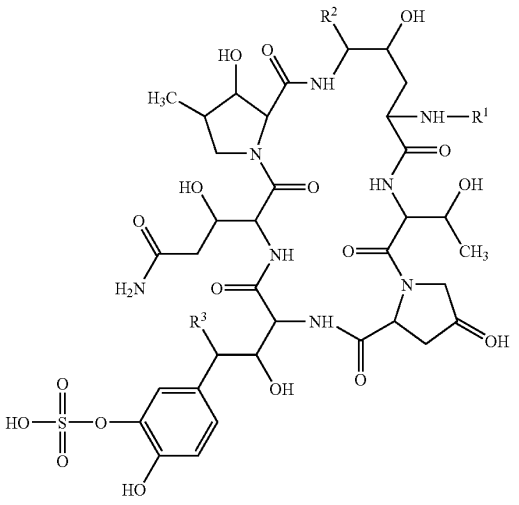
This application is a divisional of U.S. Ser. No. 09/786,125, filed Mar. 1, 2001, now U.S. Pat. No. 6,774,104, which is the national-stage under 35 U.S.C. §371 of PCT/JP00/04381, filed Jun. 29, 2000. This application also claims priority to JAPAN 11/187713, filed Jul. 1, 1999.

TECHNICAL FIELD

The present invention relates to a stabilized pharmaceutical composition in lyophilized form containing a cyclic polypeptide compound. More particularly, the present invention relates to a stabilized pharmaceutical composition in lyophilized form containing a cyclic polypeptide compound or its pharmaceutically acceptable salt and a stabilizer.

The cyclic polypeptide compound of the present invention is represented by the general formula (I):

(I)



wherein R^1 is a hydrogen atom or an acyl group and R^2 and R^3 are, the same or different, a hydrogen atom or a hydroxyl group. The compound has an antimicrobial activity, particularly an antifungal activity and a β-1,3-glucan synthase inhibiting action, and is useful for preventing and treating various kinds of infectious diseases including *Pneumocystis carinii* infection, e.g., carinii pneumonia.

BACKGROUND ART

Among the cyclic polypeptide compounds represented by the above formula (I), a compound wherein R^1 is a hydrogen atom and R^2 and R^3 are hydroxyl groups and a compound wherein R^1, R^2 and R^3 are hydrogen atoms are obtained by a fermentation process disclosed by European Patent No. 0462531 and processes disclosed by WO97/32975 and by WO97/47738. A compound wherein R^1 is an acyl group and its production process are disclosed by U.S. Pat. Nos. 5,376,634 and 5,569,646 and WO96/11210 and WO99/40108.

The cyclic polypeptide compounds (I) and their salts are generally unstable to light, humidity, acids, heat and the like.

Therefore, desired is development of pharmaceutical preparations in which the cyclic polypeptide compounds and their salts are stabilized.

DISCLOSURE OF INVENTION

The present invention provides a stabilized pharmaceutical composition in lyophilized form containing a cyclic polypeptide compound (I) or its pharmaceutically acceptable salt and a stabilizer.

The "acyl group" for R^1 in the formula (I) representing the cyclic polypeptide compound of the present invention is now explained. In the context of the present specification, "lower" means having one to six carbon atoms unless otherwise indicated.

As examples of the acyl group, may be mentioned aliphatic acyl groups, aromatic acyl groups, aromatic-aliphatic acyl groups and heterocyclic acyl groups derived from aliphatic, aromatic, aromatic-aliphatic and heterocyclic carboxylic acids.

Examples of the aliphatic acyl groups include lower or higher alkanoyl groups such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.; cycloalkanoyl groups such as cyclopentanoyl and cyclohexanoyl; lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.; lower alkanesulfonyl groups such as methanesulfonyl, ethanesulfonyl, etc.; lower alkoxysulfonyl groups such as methoxysulfonyl, ethoxysulfonyl, etc.; and the like.

Examples of the aromatic acyl groups include aroyl groups such as benzoyl, toluoyl, naphthoyl and the like.

Examples of the aromatic-aliphatic acyl groups include ar(lower)alkanoyl groups such as phenyl(C_1–C_6)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C_1–C_6)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.) and the like; ar(lower)alkenoyl group such as phenyl(C_3–C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(C_3–C_6)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc. and the like;

ar (lower)alkoxycarbonyl groups such as phenyl(C_1–C_6)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), fluorenyl(C_1–C_6)alkoxycarbonyl (e.g., fluorenylmethoxycarbonyl, etc.) and the like;

aryloxycarbonyl groups such as phenoxycarbonyl, naphthoxycarbonyl, etc.;

aryloxy(lower)alkanoyl groups such as phenoxyacetyl, phenoxypropionyl, etc.;

arylcarbamoyl groups such as phenylcarbamoyl, etc.;

arylthiocarbamoyl groups such as phenylthiocarbamoyl, etc.;

arylglyoxyloyl groups such as phenylglyoxyloyl, naphthylglyoxyloyl, etc.;

arylsulfonyl groups which may be optionally substituted by a lower alkyl group such as phenylsulfonyl, p-tolylsulfonyl, etc.; and the like.

Examples of the heterocyclic acyl groups include heterocyclic carbonyl groups such as thenoyl, furoyl, nicotinoyl, etc.;

heterocyclic(lower)alkanoyl groups such as heterocyclic acetyl, heterocyclic propanoyl, heterocyclic butanoyl, heterocyclic pentanoyl, heterocyclic hexanoyl, etc.;

heterocyclic(lower)alkenoyl groups such as heterocyclic propenoyl, heterocyclic butenoyl, heterocyclic pentenoyl, heterocyclic hexenoyl, etc.;

heterocyclic glyoxyloyl and the like.

The acyl group for R^1 may have one or more suitable substituent(s). Among the above-mentioned examples for the acyl groups, an aroyl group which may have one or more suitable substituent(s) is particularly preferable.

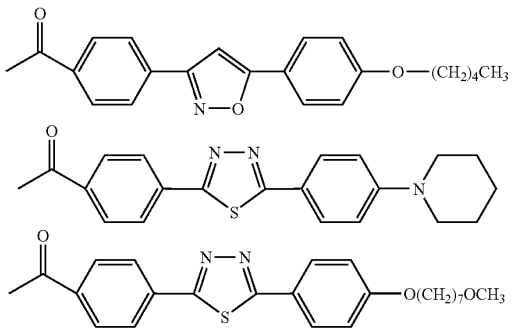
Examples of suitable substituents in the acyl group include a heterocyclic group substituted by an aryl group having a lower alkoxy group, a heterocyclic group substituted by an aryl group having a lower alkoxy(lower)alkoxy group, a heterocyclic group substituted by an aryl group having a lower alkoxy(higher)alkoxy group, a heterocyclic group substituted by an aryl group having a cyclo(lower) alkyloxy group, a heterocyclic group substituted by an aryl group having a heterocyclic group, a heterocyclic group substituted by a cyclo(lower)alkyl group having a cyclo (lower)alkyl group, a heterocyclic group substituted by an aryl group having an aryl group substituted by a lower alkoxy(lower)alkoxy and a heterocyclic group substituted by an aryl group having a heterocyclic group substituted by a cyclo(lower)alkyl group.

Among these examples, preferred are an unsaturated 3- to 8-membered heteromonocyclic group containing one to two oxygen atom(s) and one to three nitrogen atom(s) and substituted by phenyl having (C_4–C_6)alkoxy, an unsaturated condensed heterocyclic group containing one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl having (C_4–C_6)alkoxy, an unsaturated 3- to 8-membered heteromonocyclic group containing one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl having (C_1–C_4)alkoxy(C_4–C_6)alkoxy, an unsaturated 3- to 8-membered heteromonocyclic group containing one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl having (C_1–C_4)alkoxy(C_7–C_{14}) alkoxy, a saturated 3- to 8-membered heteromonocyclic group containing one to four nitrogen atom(s) and substituted by phenyl having (C_1–C_4)alkoxy(C_7–C_{14})alkoxy, an unsaturated condensed heterocyclic group containing one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl having cyclo(C_4–C_6)alkyloxy, an unsaturated condensed heterocyclic group containing one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl, a saturated 3- to 8-membered heteromonocyclic group containing one to two oxygen atom(s) and one to three nitrogen atom(s), a saturated 3- to 8-membered heteromonocyclic group having one to four nitrogen atom(s) and substituted by cyclo(C_4–C_6)alkyl having cyclo(C_4–C_6) alkyl, an unsaturated 3- to 8-membered heteromonocyclic group having one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl having phenyl substituted by (C_1–C_4)alkoxy(C_1–C_4)alkoxy, an unsaturated 3- to 8-membered heteromonocyclic group containing one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl having a saturated 3- to 8-membered heteromonocyclic group which contains one to four nitrogen atom(s) and is substituted by cyclo(C_4–C_6)alkyl, and an unsaturated condensed heterocyclic group containing one to two sulfur atom(s) and one to three nitrogen atom(s) and substituted by phenyl having a saturated 3- to 8-membered heteromonocyclic group which contains one to four nitrogen atom(s) and has cyclo(C_4–C_6)alkyl.

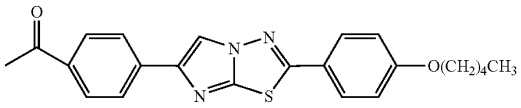
Among these, particularly preferred are an isoxazolyl group substituted by phenyl having pentyloxy, an imidazothiadiazolyl group substituted by phenyl having pentyloxy, a thiadiazolyl group substituted by phenyl having methoxyhexyloxy, a thiadiazolyl group substituted by phenyl having methoxyoctyloxy, a thiadiazolyl group substituted by phenyl having methoxyheptyloxy, an imidazothiadiazolyl group substituted by phenyl having cyclohexyloxy, an imidazothiadiazolyl group substituted by phenyl having dimethylmorpholino, a piperazinyl group substituted by phenyl having methoxyheptyloxy, a piperazinyl group substituted by phenyl having methoxyoctyloxy, a piperazinyl group substituted by cyclohexyl having cyclohexyl, a thiadiazolyl group substituted by phenyl having phenyl substituted by methoxyethoxy, a thiadiazolyl group substituted by phenyl having phenyl substituted by methoxybutoxy, a thiadiazolyl group substituted by phenyl having phenyl substituted by ethoxypropoxy, an imidazothiadiazolyl group substituted by phenyl having piperazinyl substituted by cyclohexyl, an imidazothiadiazolyl group substituted by phenyl having piperazinyl substituted by cyclohexyl, and the like.

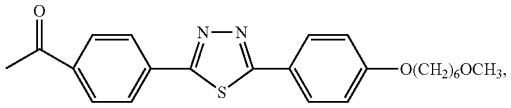
Accordingly, particularly suitable examples of the acyl group of R^1 may be a benzoyl group having isoxazolyl substituted by phenyl having pentyloxy, a benzoyl group having imidazothiadiazolyl substituted by phenyl having pentyloxy, a benzoyl group having thiadiazolyl substituted by phenyl having methoxyhexyloxy, a benzoyl group having thiadiazolyl substituted by phenyl having methoxyoctyloxy, a benzoyl group having thiadiazolyl substituted by phenyl having methoxyheptyloxy, a benzoyl group having imidazothiadiazolyl substituted by phenyl having cyclohexyloxy, a benzoyl group having imidazothiadiazolyl substituted by phenyl having dimethylmorpholino, a benzoyl group having piperazinyl substituted by phenyl having methoxyheptyloxy, a benzoyl group having piperazinyl substituted by phenyl having methoxyoctyloxy, a benzoyl group having piperazinyl substituted by cyclohexyl having cyclohexyl, a benzoyl group having thiadiazolyl substituted by phenyl having phenyl substituted by methoxyethoxy, a benzoyl group having thiadiazolyl substituted by phenyl having phenyl substituted by methoxybutoxy, a benzoyl group having thiadiazolyl substituted by phenyl having phenyl substituted by ethoxypropoxy, a benzoyl group having imidazothiadiazolyl substituted by phenyl having piperazinyl substituted by cyclohexyl, a benzoyl group having imidazothiadiazolyl substituted by phenyl having piperazinyl substituted by cyclohexyl, and the like.

Particularly preferable examples of the acyl groups of R_1 are represented by the formulas:



-continued





The cyclic polypeptide compounds (I) having the above-mentioned acyl groups may be prepared from a compound having a hydrogen atom as R_1 and hydroxyl groups as R^2 and R^3 or a compound having hydrogen atoms as R^1, R^2 and R^3 according to the U.S. Pat. Nos. 5,376,634 and 5,569,646 and WO96/11210 and WO99/40108.

Suitable salts of the cyclic polypeptide compounds (I) are soluble in water and pharmaceutically acceptable salts including salts with bases and acid addition salts. Such a salt may be prepared by treating the cyclic polypeptide compound (I) with an appropriate base or acid according to the conventional method.

As salts with bases, may be mentioned salts with inorganic bases such as alkali metal salts (e.g., sodium salts, potassium salts, etc.), alkaline earth metal salts (e.g., calcium salts, magnesium salts, etc.), ammonium salts and the like; salts with organic bases such as organic amine salts (e.g., triethylamine salts, diisopropylethylamine salts, pyridine salts, picoline salts, ethanolamine salts, triethanolamine salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts, etc.); and the like.

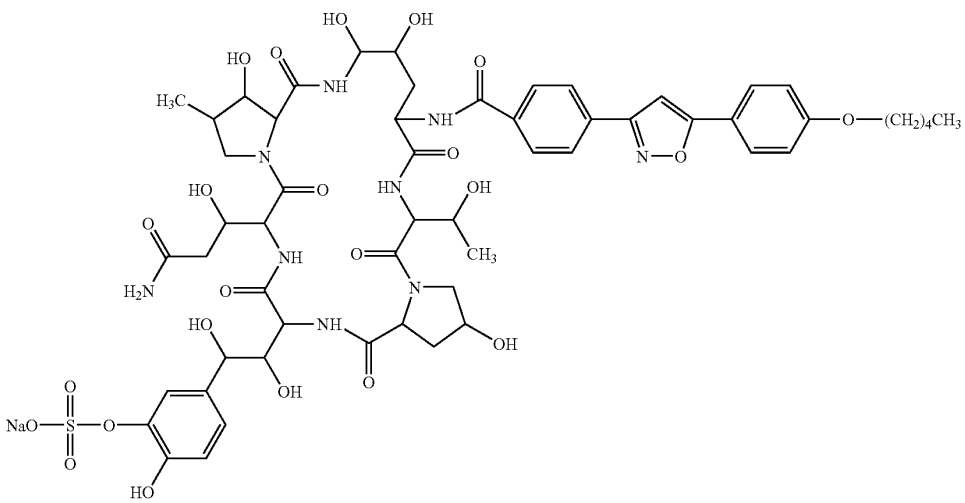
As acid addition salts, may be mentioned inorganic acid addition salts (e.g., hydrochlorides, hydrobromides, sulfates, phosphates, etc.); and organic carboxylic or sulfonic acid addition salts (e.g., formates, acetates, trifluoroacetates, maleates, tartrates, fumarates, methnesulfonates, benzenesulfonates, toluenesulfonates, etc.). Further, may also be mentioned salts with basic or acidic amino acids (e.g., salts with arginine, aspartic acid, glutamic acid, etc.).

The cyclic polypeptide compounds (I) of the present invention also include possible conformers and a pair or more of stereoisomers such as geometric isomers and optical isomers which may exist due to asymmetric carbon atoms.

The preferable ones of the cyclic polypeptide compounds (I) are represented by the following formulas (II) to (VI):

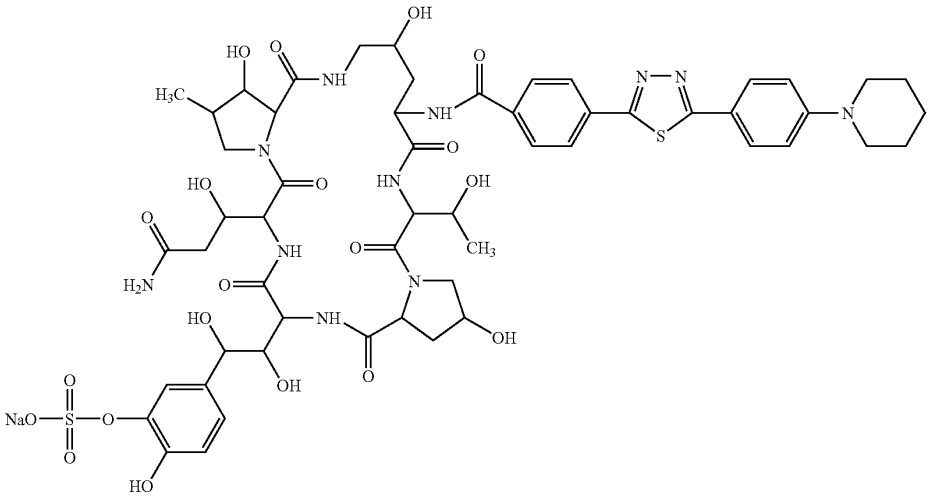
(to be continued on the next page)

(II)

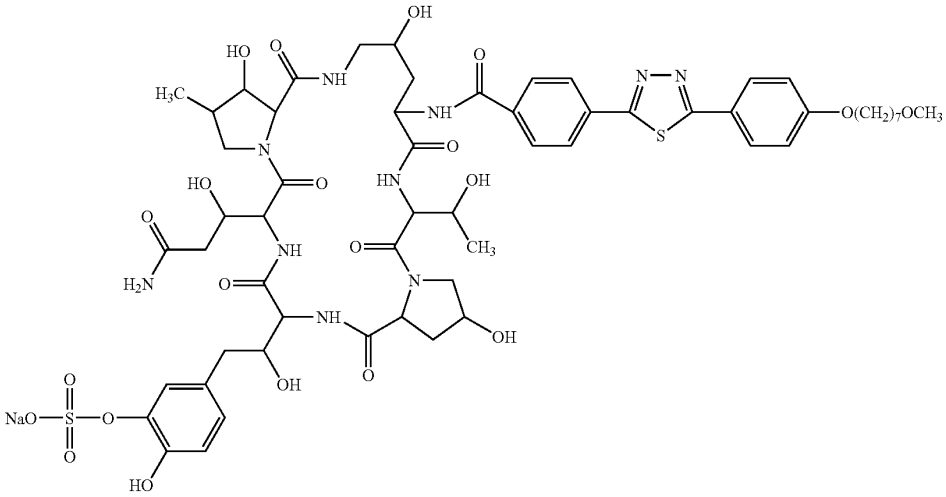


-continued

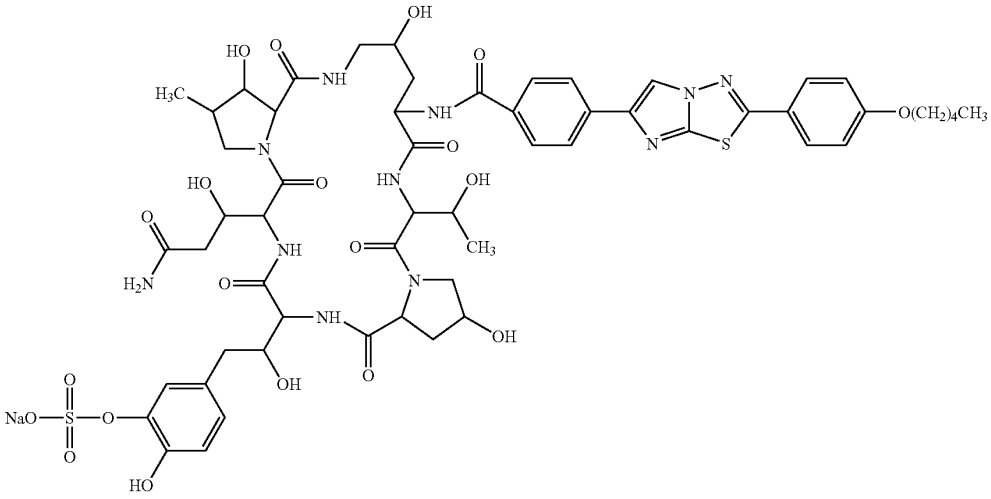
(III)



(IV)



(V)



DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.