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HOFFMANN-LA ROCHE INC.

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

HOFFMANN-LA ROCHE INC., Plaintiff, v. ACCORD HEALTHCARE INC. and INTAS PHARMACEUTICAL LTD., Defendants.	Civil Action No. _____ **VERIFIED COMPLAINT**

Plaintiff Hoffmann-La Roche Inc. ("Roche") brings this Verified Complaint against Accord Healthcare Inc. ("Accord") and Intas Pharmaceutical Ltd. ("Intas") (collectively "Defendants"), and says:

NATURE OF THE ACTION

1. This is an action for infringement of Claim 6 of United States Patent No. 5,472,949 ("the '949 patent"). Roche brings this action to enforce its patent rights covering Xeloda® capecitabine 150 mg and 500 mg tablets, the first oral chemotherapy drug approved in the United States. Xeloda® has been approved in the United States for the treatment of breast and colorectal cancer and Dukes' C Stage III colon cancer. A copy of the '949 patent is attached to this Complaint as Exhibit A.

PARTIES

2. Roche is a company organized and existing under the laws of the State of New Jersey with its principal place of business at 340 Kingsland Street, Nutley, New Jersey 07110.

3. On information and belief, Accord is a corporation organized under the laws of North Carolina, with its principal place of business at 1009 Wilson Road, Suite 210-B, Durham, North Carolina 27703.

4. On information and belief, Accord is in the business of selling generic pharmaceutical products, which it distributes in the State of New Jersey and throughout the United States.

5. On information and belief, Accord is licensed with the New Jersey Department of Health and Senior Services as a seller of pharmaceuticals in the State of New Jersey.

6. On information and belief, generic drug products developed and manufactured by Accord and approved by the FDA are for sale and are sold in the State of New Jersey, including eleven (11) approved pharmaceuticals listed on the New Jersey Medicare formulary.

7. Accord has previously submitted to the jurisdiction of this Court in *Astrazeneca Pharmaceuticals LP, et al. v. Accord Healthcare, Inc., et al.*, Civil Action No. 3:08-cv-04804-JAP-TJB and *Astrazeneca Pharmaceuticals LP v. Accord Healthcare, Inc., et al.*, Civil Action No. 3:09-cv-00619-JAP-TJB.

8. Accord has availed itself of the legal protections of the State of New Jersey, having asserted counterclaims filed in this jurisdiction.

9. On information and belief, Intas is a corporation organized under the laws of India, with its principal place of business at Chinubhai Centre Off. Nehru Bridge Ashram Road, Ahmedabad 380009, Gujarat, India.

10. On information and belief, Intas is in the business of manufacturing and selling generic pharmaceutical drugs that are marketed and distributed by Accord in New Jersey and throughout the United States.

11. Intas has previously submitted to the jurisdiction of this Court in *Astrazeneca Pharmaceuticals LP, et al. v. Accord Healthcare, Inc., et al.*, Civil Action No. 3:08-cv-04804-JAP-TJB and *Astrazeneca Pharmaceuticals LP v. Accord Healthcare, Inc., et al.*, Civil Action No. 3:09-cv-00619-JAP-TJB.

12. Intas has availed itself of the legal protections of the State of New Jersey, having asserted counterclaims filed in this jurisdiction.

13. On information and belief, Accord is a wholly-owned subsidiary and agent of Intas.

14. On information and belief, the acts of Accord complained of herein were done upon the initiation, direction and control of, and with the authorization of, and/or with the cooperation, participation and assistance of Intas.

JURISDICTION AND VENUE

15. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

16. On information and belief, Defendants are in the business of formulating, manufacturing, marketing and/or selling generic pharmaceutical drugs that they distribute in New Jersey and throughout the United States. Defendants, either directly and/or through one or more of their agents or distributors, sell and/or distribute a substantial volume of their pharmaceutical products in New Jersey.

17. This Court has personal jurisdiction over Defendants because, *inter alia*, Defendants have previously submitted to jurisdiction in this Court, and have availed themselves of the jurisdiction of this Court by asserting counterclaims in lawsuits filed in the United States District Court for the District of New Jersey and have maintained continuous and systematic contacts with the State of New Jersey.

18. Venue is proper in this District under 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT IN SUIT

19. On December 5, 1995, the '949 patent, titled "N^4-(Substituted-Oxycarbonyl)-5'-Deoxy-5-Fluorocytidine Compounds, Compositions and Methods of Using Same," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Roche is the lawful owner by assignment of all rights, title and interest in and to the '949 patent, including all rights to sue and recover for infringement thereof.

20. The '949 patent covers N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine compounds, compositions and methods of using same. Capecitabine is a N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine compound. The Xeloda® drug product contains capecitabine.

STATEMENT OF FACTS COMMON TO ALL COUNTS

21. This action arises from Accord's efforts to gain approval from the FDA to market a generic version of Roche's Xeloda® brand capecitabine drug products prior to the expiration of Roche's '949 patent . The FDA approved Roche's Xeloda® brand capecitabine drug product for marketing in the United States under Roche's New Drug Application ("NDA") No. 20-896, pursuant to section 505(b) of the Federal Food, Drug, and Cosmetics Act ("FFDCA"), 21 U.S.C. § 355(b).

22. With the passage of the Hatch-Waxman Act in 1984, the FFDCA provisions with respect to the generic drug approval process were amended in several important respects. One provision requires innovator drug companies to submit patent information to the FDA "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1). The FDA then publishes the submitted patent information in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly referred to as the "Orange Book").

23. In compliance with that statutory obligation, Roche submitted patent information to the FDA in connection with its NDA No. 20-896 for Roche's Xeloda® brand capecitabine drug product, and the FDA has published the same in the Orange Book.

24. The Hatch-Waxman Act further amended the FFDCA to permit drug companies to gain approval of generic copies of innovator drugs (also called the "reference drug") by referencing studies performed by the innovator, without having to expend the same considerable investment in time and resources as does the innovator company. Thus, generic drug companies are permitted to file what is referred to as an Abbreviated New Drug Application ("ANDA") under 21 U.S.C. § 355(j). When filing an ANDA, generic drug companies are required to review the patent information that the FDA listed in the Orange Book for the reference drug and make a statutory certification (commonly called "patent certification") with respect to same.

25. As relevant here, the generic drug company may seek FDA approval to market its generic drug product prior to patent expiration by alleging in its ANDA that the listed patent(s) is/are "invalid or will not be infringed" (commonly called a "Paragraph IV certification"). 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

26. The '949 patent is listed in the Orange Book as a patent "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1).

27. On information and belief, Accord has filed ANDA No. 202593 with the FDA seeking approval to market 150 mg and 500 mg generic copies of Roche's Xeloda® brand capecitabine drug products prior to expiration of Roche's '949 patent.

28. On or about February 17, 2011, Roche received a letter from Dr. Samir Mehta, President of Accord Healthcare Inc., purporting to be a notice of Accord's filing an ANDA seeking to market a generic copy of Roche's Xeloda® brand capecitabine drug products and allegedly containing a Paragraph IV certification as required by 21 U.S.C. §§ 355(j)(2)(B)(i) and (ii) with respect to Roche's '949 patent.

29. Accord's Paragraph IV Notice to Roche states Accord's intention to seek FDA approval to market generic versions of Roche's Xeloda® brand capecitabine drug products prior to expiration of Roche's '949 patent, which expires at midnight on December 14, 2013. Notwithstanding the U.S. PTO's grant of the '949 patent to Roche, Accord asserts in its Paragraph IV Notice that the '949 patent is invalid.

30. Accord's efforts to seek FDA approval to market a generic copy of Roche's Xeloda® brand capecitabine drug products prior to expiration of Roche's '949 patent constitutes an act of infringement and, thus, creates a justiciable controversy between Roche and Defendants with respect to the subject matter of Accord's purported ANDA and the validity and infringement of Roche's '949 patent.

31. Accord filed its ANDA for a generic copy of Roche's Xeloda® brand capecitabine drug products because Defendants seek to enter the capecitabine market that Roche has created by providing advantageous treatment for breast and colorectal cancer and Dukes' C stage III colon cancer.

COUNT ONE

Infringement of Claim 6 of the '949 Patent Under 35 U.S.C. § 271(e)(2)

32. Roche alleges paragraphs 1 through 31 above as if set forth herein.

33. On information and belief, Accord included a Paragraph IV certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with ANDA No. 202593 alleging that the '949 patent is invalid.

34. Upon information and belief, Intas initiated, directed and controlled the activities of Accord with regard to ANDA No. 202593 and the capecitabine drug product described therein.

35. Pursuant to 35 U.S.C. § 271(e)(2)(A), Defendants Intas and Accord committed an act of infringement by filing with the FDA ANDA No. 202593 with a Paragraph IV certification that seeks FDA marketing approval for a generic copy of Roche's Xeloda® brand capecitabine drug products prior to expiration of Roche's '949 patent.

36. Any commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' generic capecitabine drug products prior to expiration of the '949 patent will infringe Claim 6 of Roche's '949 patent under 35 U.S.C. § 271(e)(4)(C).

37. Roche is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an Order of this Court that the effective date of approval for Defendants' ANDA No. 202593 be a date that is not earlier than the expiration date of the '949 patent, which is currently December 14, 2013.

38. Roche will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Roche does not have an adequate remedy at law.

COUNT TWO

Infringement of Claim 6 of the '949 Patent Under 35 U.S.C. § 271(b)

39. Roche alleges paragraphs 1 through 38 above as if set forth herein.

40. On information and belief, Intas actively induced Accord to submit ANDA No. 202593 to the FDA to obtain approval under the FFDCA to engage in the commercial manufacture, use, or sale throughout the United States including New Jersey of Accord's generic copy of Roche's Xeloda® brand capecitabine drug products. By actively inducing submission of the ANDA, Intas has committed an act of indirect infringement with respect to Claim 6 of the '949 patent under 35 U.S.C. § 271(b).

41. Any commercial manufacture, use, offer for sale, and/or importation of Accord's generic copy of Roche's Xeloda® brand capecitabine drug products prior to patent expiry will infringe Claim 6 of the '949 patent under 35 U.S.C. § 271(a) and Intas' conduct will actively induce such infringement under 35 U.S.C. § 271(b).

COUNT THREE

Declaratory Judgment of Infringement of Claim 6 of the '949 Patent Under 35 U.S.C. § 271

42. Roche alleges paragraphs 1 through 41 above as if set forth herein.

43. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

44. Roche is entitled to a declaration that, if Defendants, prior to patent expiry, commercially manufacture, use, offer for sale or sell Accord's proposed generic version of Xeloda® brand capecitabine drug product within the United States, import Accord's proposed generic version of Xeloda® brand capecitabine drug product into the United States, or induce or contribute to such conduct, Defendants would infringe Claim 6 of the '949 patent under 35 U.S.C. § 271(a), (b) and/or (c).

45. Roche will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Roche does not have an adequate remedy at law.

EXCEPTIONAL CASE

46. The actions of Defendants, individually and collectively, render this an exceptional case under 35 U.S.C. § 285, and therefore Roche is entitled to an award of reasonable attorneys fees from Defendants because their failure to adhere to appropriate legal standards in the Paragraph IV Notice letter.

INJUNCTIVE RELIEF

47. Roche will be irreparably harmed by infringing activities of Defendants unless those activities are enjoined by this Court. Roche does not have an adequate remedy at law.

RELIEF SOUGHT

WHEREFORE, Plaintiff requests:

A) A judgment and decree that Claim 6 of the '949 patent is valid and enforceable;

B) A judgment that Defendants infringed Claim 6 of Roche's '949 patent under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 202593 with a Paragraph IV certification seeking to market generic versions of Xeloda® capecitabine drug products prior to the expiration of the '949 patent;

C) A judgment that Intas infringed Claim 6 of Roche's '949 patent under 35 U.S.C. § 271(b) by actively inducing Accord to infringe Roche's '949 patent under 35 U.S.C. § 271(e)(2)(A);

D) An Order pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Accord's ANDA No. 202593 be a date that is not earlier than the expiration date of the '949 patent, which is currently December 14, 2013;

E) A judgment that the commercial manufacture, use, offer for sale, sale, and/or importation of Accord's generic version of Xeloda® capecitabine drug products prior to the expiration of the '949 patent will constitute an act of infringement of the said patent under § 271;

F) A judgment declaring that if Defendants, their respective officers, agents, servants, employees, licensees, and representatives, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf, engage in the commercial manufacture, use, offer for sale, sale, and/or importation of generic versions of Xeloda® capecitabine drug products prior to the expiration of the '949 patent, such conduct will constitute an act of infringement of Claim 6 of the '949 patent under § 271;

G) A permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) restraining and enjoining Defendants and their respective officers, agents, servants and employees, licensees, and representatives and those persons in acting or attempting to act in active concert or participation with any of them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States of their generic versions of Xeloda® capecitabine drug products prior to December 15, 2013, the day after the current expiration of the '949 patent;

H) An award of attorneys' fees under 35 U.S.C. § 285; and

I) Such other and further relief as the Court may deem just and proper.

Respectfully submitted,

GIBBONS P.C.

Dated: June 24, 2011
Newark, New Jersey

s/ Sheila F. McShane
By: David E. De Lorenzi, Esq.
Sheila F. McShane, Esq.

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Attorneys for Plaintiff
HOFFMANN-LA ROCHE INC.

VERIFICATION

I, Sheila F. McShane, have read the foregoing Verified Complaint, and declare pursuant to 28 U.S.C. § 1746, under penalty of perjury, that the foregoing information stated therein is true and correct to the best of my knowledge, information and belief.

Date: June 24, 2011

s/Sheila F. McShane
Sheila F. McShane

EXHIBIT A

US005472949A

United States Patent [19]

Arasaki et al.

[11] Patent Number: 5,472,949

[45] Date of Patent: Dec. 5, 1995

[54] N^4-(SUBSTITUTED-OXYCARBONYL)-5'-DEOXY-5-FLUOROCYTIDINE COMPOUNDS, COMPOSITIONS AND METHODS OF USING SAME

[75] Inventors: **Motohiro Arasaki; Hideo Ishitsuka; Isami Kuruma; Masanori Miwa; Chikako Murasaki; Nobuo Shimma; Isao Umeda**, all of Kanagawa, Japan

[73] Assignee: **Hoffmann-La Roche Inc.**, Nutley, N.J.

[21] Appl. No.: **167,392**

[22] Filed: **Dec. 14, 1993**

[30] **Foreign Application Priority Data**

Dec. 18, 1992 [EP] European Pat. Off. 92121538

[51] **Int. Cl.**[6] **A61K 31/70**; C07H 19/06

[52] **U.S. Cl.** **514/49**; 536/28.5; 536/28.52

[58] **Field of Search** 514/49, 50; 536/28.5, 536/28.52

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,966,891 10/1990 Fujiu et al. 514/49

OTHER PUBLICATIONS

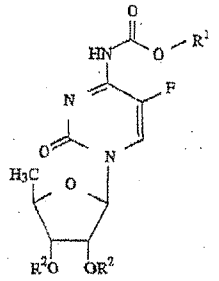
Umeda et al., "Synthesis and antitumor activity of 5'-deoxy-5-fluorocytidine (5'-DFCR) derivatives", J. Pharmacobio-Dyn., 13:s-144 (1990).

Primary Examiner—Douglas W. Robinson
Assistant Examiner—James O. Wilson
Attorney, Agent, or Firm—George M. Gould; George W. Johnston; Robert A. Silverman

[57] **ABSTRACT**

The invention relates to N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine derivatives which are useful as an agent for treating tumors, pharmaceutical compositions including the same, a method of treating tumors and a method of preparing N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine derivatives for treating tumors.

Compounds of formula (I),



(I)

wherein R^1 is a saturated or unsaturated, straight or branched hydrocarbon radical wherein the number of carbon atoms in the longest straight chain of this hydrocarbon radical ranges from three to seven, or is a radical of the formula $-(CH_2)n-^Y$ wherein Y is a cyclohexyl radical, a C_1–C_4 alkoxy radical or a phenyl radical and wherein when Y is a cyclohexyl radical n is an integer from 0 to 4, and when Y is C_1–C_4 alkoxy radical or a phenyl radical n is an integer from 2 to 4, and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

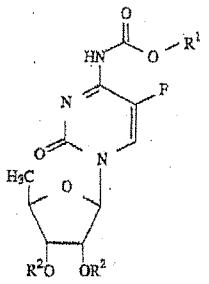
or a hydrate or solvate thereof. Compounds of formula (I) are useful in the treatment of tumors.

6 Claims, No Drawings

N^4-(SUBSTITUTED-OXYCARBONYL)-5'-DEOXY-5-FLUOROCYTIDINE COMPOUNDS, COMPOSITIONS AND METHODS OF USING SAME

SUMMARY OF INVENTION

The invention relates to N^4-(substituted-oxycarbonyl)-5'-deoxy-5- fluorocytidine derivatives of formula (I),



(I)

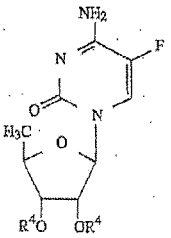
wherein R^1 is a saturated or unsaturated, straight or branched hydrocarbon radical wherein the number of carbon atoms in the longest straight chain of the hydrocarbon radical ranges from three to seven, or is a radical of the formula $—(CH_2)_n—Y$ wherein Y is a cyclohexyl radical, a C_1–C_4 alkoxy radical or a phenyl radical and n is an integer from 0 to 4; and when Y is a C_1–C_4 alkoxy radical or a phenyl radical n is an integer from 2 to 4, and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

or a hydrate or solvate thereof. The compound is useful for treating tumors.

In another aspect, the invention relates to a pharmaceutical composition including an effective amount of at least one compound of formula (I). The pharmaceutical composition has excellent pharmacokinetic profiles for treating tumors with high safety margin.

In yet a further aspect, the invention relates to a method of treating tumors comprising administering to a host in need of such treatment an effective amount of a compound of formula (I).

In yet another aspect, the invention relates to a process for producing a N4-(substituted-oxycarbonyl)-5'-fluorocytidine derivatives which comprises reacting a compound of formula (II).



(II)

wherein R^4 is a hydroxy-protecting radical, with a compound of formula (III)

R^1OCOCl (III)

and, optionally, removing R^4.

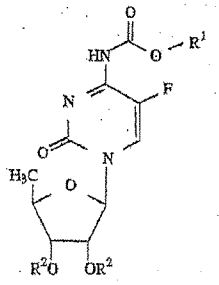
BACKGROUND OF THE ART

It is known that many precursors of 5-fluorouracil (5-FU) are useful as antitumor agents, but in general their bioconversion efficiency is still insufficient for the treatment of patients suffering from tumors. Further they cause intestinal toxicities and immunosuppressive toxicities, which are their major and dose limiting toxicities, respectively.

U.S. Pat. No. 4,966,891 discloses precursors of 5-FU which are improved in the above mentioned aspect of bioconversion efficiency and toxicities. They are converted to 5'-deoxy-5-fluorocytidine (5'-DFCR) by acylamidases, to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, and then to 5-FU by pyrimidine nucleotide phosphorylase in vivo which is preferentially localized in the liver, small intestin and tumor tissues.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to compounds of formula (I),



(I)

wherein R^1 is a saturated or unsaturated, straight or branched hydrocarbon radical wherein the number of carbon atoms in the longest straight chain of this hydrocarbon radical ranges from three to seven, or is a radical of the formula $—(CH_2)_n—Y$ wherein Y is a cyclohexyl radical, a C_1–C_4 alkoxy radical or a phenyl radical and wherein when Y is a cyclohexyl radical n is an integer from 0 to 4, and when Y is C_1–C_4 alkoxy radical or a phenyl radical n is an integer from 2 to 4, and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

or a hydrate or solvate thereof. Compounds of formula (I) are useful in the treatment of tumors.

In the above, the term a saturated or unsaturated, straight or branched hydrocarbon radical wherein the number of carbon atoms in the longest straight chain of this hydrocarbon radical ranges from three to seven preferably is n-propyl, 1-isopropyl-2-methylpropyl, 1,1,2-trimethylpropyl, n-butyl, isobutyl, 2-ethylbutyl, 3,3-dimethylbutyl, n-pentyl, isopentyl, neopentyl, 2-propylpentyl, n-hexyl, 2-ethylhexyl, n-heptyl, allyl, 2-buten-1-yl, 3-buten-1-yl, 3-penten-1-yl, 4-penten-1-yl, 3-hexen-1-yl, 4-hexen-1-yl, 5-hexen-1-yl, and the like.

The term a radical of the formula $—(CH_2)_n—Y$ [in which n is an integer from 0 to 4, when Y is a cyclohexyl radical, or n is an integer from 2 to 4, when Y is a lower alkoxy radical having from 1 to 4 carbon atom(s) or a phenyl radical preferably is cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 3-cyclohexylpropyl, 4-cyclohexylbutyl, 2-methoxyethyl, 2-ethoxyethyl, 2-propoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, 4-methoxybutyl, 4-ethoxybutyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, and the like.

Most preferably, R^1 is n-propyl, n-butyl, n-pentyl, isopentyl, neopentyl, 3,3-dimethylbutyl, n-hexyl, 2-ethylbutyl, phenylethyl, or cyclohexylmethyl.

In the above, the term a radical easily hydrolyzable under physiological condition preferably denotes acetyl, propionyl, benzoyl, toluoyl, β-alanyl, valyl, and the like.

Preferred N^4-(substituted-oxycarbonyl)-5'-DFCRs of the invention are:

5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine,

N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-(pentyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(hexyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(isopentyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(neopentyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-[(1,1,2-trimethylpropoxy)carbonyl]cytidine,

5'-deoxy-N^4-[(3,3-dimethylbutoxy)carbonyl]-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-[(1-isopropyl-2-methylpropoxy-)carbonyl]cytidine,

5'-deoxy-N^4-[(2-ethylbutoxy)carbonyl]-5-fluorocytidine,

N^4-[(cyclohexylmethoxy)carbonyl]-5'-deoxy-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-[(2-phenylethoxy)carbonyl]cytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine,

2',3'-di-acetyl-N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine,

2',3'-di-benzoyl-N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(pentyloxycarbonyl)cytidine,

2',3'-di-acetyl-5'-deoxy-5-fluoro-N^4-(isopentyloxycarbonyl)cytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(hexyloxycarbonyl)-cytidine,

2',3'-di-O-acetyl-5'-deoxy-N^4-[(2-ethylbutyl)oxycarbonyl]-5 -fluorocytidine,

2',3'-di-O-acetyl-N^4-[(cyclohexylmethoxy)carbonyl]-5'-deoxy-5-fluorocytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-[(2-phenylethoxy-)carbonyl]cytidine,

5'-deoxy-5-fluoro-N^4-(isobutoxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-[(2-propylpentyl)oxycarbonyl]cytidine,

5'-deoxy-N^4-[(2-ethylhexyl)oxycarbonyl]-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-(heptyloxycarbonyl)cytidine,

N^4-[(2-cyclohexylethoxy)carbonyl]-5'-deoxy-5-fluorocytidine,

N^4-[(3-cyclohexylpropyl)oxycarbonyl]-5'-deoxy-5-fluorocytidine,

N^4-(cyclohexyloxycarbonyl)-5'-deoxy-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-[(3-phenylpropyl)oxycarbonyl]cytidine, and

5'-deoxy-5-fluoro-N^4-[(2-methoxyethoxy)carbonyl]cytidine.

and their hydrates or solvates, and the like.

Among the above compounds, particularly preferred N^4-(substituted-oxycarbonyl)-5'-DFCRs of the invention are:

5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(isopentyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(hexyloxycarbonyl)cytidine,

5'-deoxy-N^4-[(2-ethylbutyl)oxycarbonyl]-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-(neopentyloxycarbonyl)cytidine,

5'-deoxy-N^4-[(3,3 -dimethylbutoxy)carbonyl]-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-[(2-phenylethoxy)carbonyl]cytidine,

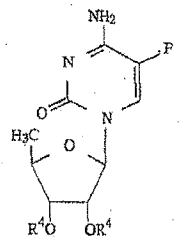
N^4-[(cyclohexylmethoxy)carbonyl]-5'-deoxy-5-fluorocytidine, specially

N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-(pentyloxycarbonyl)cytidine, and their hydrates or solvates, and the like.

Studies on the pharmacokinetic profiles of the precursors of 5-FU, particularly of N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine derivatives, showed that certain specific precursors are selectively converted into 5'-DFCR by an acylamidase isozyme that is preferentially located at the liver but not the other organs of humans, and exhibited more improved pharmacokinetic profiles than the other compounds tested. Further studies based on the above findings enabled identification that the specific N^4-(substituted-oxycarbonyl)-5'-deoxy-5- fluorocytidine derivatives (hereinafter referred to as N^4-(substituted-oxycarbonyl)-5'-DFCR) of formula (I) have selectively im pharmacokinetic profiles in monkeys, that is, 4 to 7 times higher maximum concentration (C_{max}) of 5'-DFUR and 4 times larger higher area under the curve (AUC) of 5'-DFUR in blood than the other compounds, and less intestinal toxicity.

The N^4-(substituted-oxycarbonyl)-5'-DFCRs of formula (I) as well as their hydrates or solvates can be prepared by a reaction of a compound of formula (II),



(II)

wherein R^4 is a hydroxy-protecting radical such as acetyl, benzoyl, trimethylsilyl, tert-butyldimethylsilyl, and the like,

with a compound of formula (III),

$$R^1OCOCl \qquad \text{(III)}$$

wherein R^1 is the same as defined above,

followed, if necessary, by removal of a protecting radical.

The compounds of formula (II) can be prepared by 2',3'-di-O-acylation or silylation of 5'-deoxy-5-fluorocytidine [*J. Med. Chem.*, 22, 1330 (1979)]as described in U.S. Pat. No. 4,966,891 or by direct coupling of 5-fluorocytosine with 1,2,3-tri-O-acetyl-5-deoxyribofuranose according to the procedure similar to that described in *Synthesis*, 748 (1981).

The reaction of the compound of formula (II) with the compound of formula (III) can be carried out in a solvent such as pyridine, dioxane, tetrahydrofuran, acetonitrile,

chloroform, dichloromethane and the like in the presence of acid acceptor such as triethylamine, pyridine, picoline, 4-(N, N-dimethylamino)pyridine, lutidine and the like. The reaction can be carried out at a temperature between 0° and 30° C.

The protecting radical may, if necessary, be removed after the reaction by the procedures known to those skilled in the art [*Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, *Can. J. Chem.*, 49, 493 (1971) and U.S. Pat. No. 4,966,891], for example by basic or acidic hydrolysis.

The compounds of formula (I) can exist as unsolvated as well as solvated forms, including hydrated forms. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially anhydrous product. Solyates with pharmaceutically acceptable solvents such as ethanol can be obtained during, for example, crystallization.

N^4-(Substituted-oxycarobonyl)-5'-DFCR derivatives of formula (I) as well as hydrates or solyates thereof prepared by the above process exhibit activity against human colon cancer CXF280 and gastric cancer GXF97 xenografts, mouse colon 26 carcinoma, mouse Lewis lung carcinoma, and the like in mice over a very wide range of dosages both orally and parenterally and are useful as antitumor agents. They are efficiently converted to 5'-DFCR by an acylamidase isozyme, to 5'-DFUR by cytidine deaminase and then to the active metabolite 5-FU by pyrimidine nucleoside phosphorylase.

The invention further relates to a pharmaceutical composition for the treatment of tumors. The pharmaceutical composition comprises an effective amount of one or more compounds of formula (I).

The N^4-(substituted-oxycarbonyl)-5'-DFCRs of the invention can be administered orally or non-orally to hosts by various conventional administration methods. Moreover, the N^4-(substituted-oxycarbonyl)-5'-DFCRs according to the invention are used singly or formulated with a compatible pharmaceutical carrier material. This carrier material can be an organic or inorganic inert carrier material suitable for enteral, percutaneous or parenteral administration such as, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene-glycols or petroleum jelly. The pharmaceutical composition can be made up in a solid form, for example, as tablets, drages, enteric coating tablets, granulars, enteric coating granulars, suppositories, capsules or enteric capsules, in a semi-solid form, for example, as salves, or in a liquid form, for example, as solutions, suspensions or emulsions. The pharmaceutical composition may be sterilized and/or may contain further adjuvants such as preserving, stabilizing, setting or emulsifying agents, flavor-improving agents, salts for variation of the osmotic pressure or substances acting as buffers. The pharmaceutical composition can be prepared in a conventional manner.

The N^4-(substituted-oxycarbonyl)-5'-DFCRs according to the present invention can be used alone or as mixtures of two or more different N^4-(substituted-oxycarbonyl)-5'-DFCRs and the amount of the N^4-(substituted-oxycarbonyl)-5'-DFCRs is about 0.1 to 99.5%, preferably 0.5 to 95%, based on the weight of the pharmaceutical composition.

The pharmaceutical composition according to the present invention may be formulated in a combination with other conventional antitumor agent.

The invention also relates to a method of treating tumors comprising administering to a host in need of such treatment an effective amount of at least one compound of formula (I).

Susceptibility to acylamidase of the N^4-(substituted-oxycarbonyl)- 5'-DFCRs of the invention and their pharmacokinetic profil monkey are shown below:

1. Susceptibility to human and monkey acylamidases

The N^4-(substituted-oxycarbonyl)-5'-DFCRs of the invention were incubated with crude extracts of monkey and human liver in the presence of an inhibitor of cytidine deaminase, tetrahydrouridine (0.4 mM) at 37° C. for 60 min. Thereafter, the product 5'-DFCR was separated by HPLC and the enzyme susceptibility was calculated from the amount of the product. As Table 1 shows, the compounds of formula (I) were highly susceptible to the human liver acylamidase, suggesting that they are efficiently biotransformed to 5'-DFCR in human.

TABLE 1

Susceptibility to monkey and human acylamidase in the liver

Compound (Example No.)	Acylamidase activity (nmol/mg protein/hr) Monkey Liver	Human Liver
11	20	71
12	29	190
13	47	220
14	32	74
15	23	210
16	33	210
17	22	160
20	19	320
21	26	82
22	43	110
24	18	64
25	<13	160
26	20	560
27	59	110
28	25	52
29	22	50

2. Pharmacokinetic profiles in monkeys

The compounds of formula (I) were orally administered into groups of 2 to 5 cynomolgous monkeys (3~4 kg). At various times after the administration, plasma was taken for determination of blood concentrations of intact molecules and their active metabolite 5'-DFUR.

Metabolites in the plasma were separated by HPLC and their concentrations were calculated. As Table 2 shows, the compounds of the present invention gave high levels in C_{max} and AUC of the active metabolite 5'-DFUR in the plasma. These results indicate that the compounds of the invention can be effectively utilized for the treatment of various tumors in human beings.

TABLE 2

Pharmacokinetic Profiles in Monkeys

Compound (Example No.)	Plasma 5'-DFUR Cmax (μg/ml)	AUC (μg · hr/ml)
10	1.44	2.03
11	1.57	2.06
12	2.10	2.90
13	1.50	1.96
14	1.80	2.40
15	2.60	2.89
16	1.40	2.52
17	1.65	2.66
28	1.00	1.40
29	2.00	2.09

The antitumor activities of the compounds of the invention are shown as follows:

3. Antitumor testing against human colon cancer xenograft CXF280

CXF280 tumor (about 2×2 mm piece) was implanted subcutaneously into BALB/c nu/nu mice (21–22 g) on day 0. When tumor volume became 100 mm^3 on day around 14, the compounds of the invention were orally administered daily for 3 weeks. At one day after the last treatment, tumor volume was calculated.

TABLE 3

Antitumor Effects of Fluorinated Pyrimidines in BALB/c nu/nu Mice Bearing CXF280 Human Colon Carcinoma

Compound (Example No.)	Dose × 21 (mmol/kg/day)	% Growth inhibition	Fecal observation*
Exp. 1			
Vehicle		—	N
12	0.13	68	
	0.3	69	
	0.67	86	
	1.0	86	
	1.5	96	N
13	0.13	59	
	0.3	66	
	0.67	79	
	1.0	91	
	1.5	94	N
24	0.13	37	
	0.3	64	
	0.67	75	
	1.0	83	
	1.5	89	N
Reference compound			
5-FU	0.089	28	N
	0.13	59	N
	0.2	79	L
Exp. 2			
Vehicle		—	N
10	0.13	39	
	0.3	56	
	0.67	75	
	1.5	86	
	2.25	93	N
11	0.13	46	
	0.3	72	
	0.67	84	
	1.5	95	
	2.25	100	N
14	0.13	68	
	0.3	68	
	0.67	85	
	1.5	94	N
	2.25	100	N
27	0.13	26	
	0.3	72	
	0.67	84	
	1.5	94	N
	2.25	103	N
Reference compound			
5-FU	0.089	NE	N
	0.13	20	N
	0.2	58	L

NE: Not Effective,
*Fecal observation (N: normal feces, L: loose passage)

The percent inhibition of tumor growth given in Table 3 above was calculated from the formula:

$$\% \text{ Inhibition} = \{1-(T-V_0)/(C-V_0)\}\times 100$$

V_0=volume of tumor before treatment was started, T=volume of the tumors from the treated group, C=volume of the tumor from the control group.

As Table 3 shows, the compounds provided in the present invention were safely administered without causing intestinal toxicity and were much more effective than 5-FU.

4. Antitumor and anticachexia activity against mouse colon 26 carcinoma

Antitumor activity of a representative compound (Example 13), of the present invention, was measured as follows. Mice (CDF_1) were subcutaneously inoculated with colon 26 carcinoma (10^6 cells) on day 0. The compound was administered daily for 7 times from day 21 when the animals became cachectic. One day after the last treatment, tumor weight gain, carcass weight gain, adipose tissue weight, concentrations of glucose and the acute phase reactant IAP (immunosuppressive acidic protein) in the serum were measured. As Table 4 shows, mice treated with vehicle were abnormal in cachexia parameters such as adipose tissue weight, serum glucose and IAP levels, whereas treatment with the compound of Example 13 suppressed tumor growth and improved cachexia.

TABLE 4

Improvement of Tumor Cachexia with Fluorinated Pyrimidines in Mice Bearing Colon 26 Adenocarcinoma

Compound (Example No.)	Dose × 7 (mmol/kg) (μg/ml)	Tumor wt. change (g)	Carcass wt. change (g)	Adipose tissue wt. (mg)	Serum glucose (mg/dl)	Serum IAP
Vehicle		1.65	−1.5	11	91	1167
13	0.125	1.24	1.6*	22*	118*	1195
	0.25	0.91	3.4*	42*	120*	1020
	0.5	0.79*	4.2*	63*	147*	805*
	1	0.006	5.6*	85*	127*	795*

*P < 0.05 versus corresponding value of vehicle group

The toxicity (LD_{50}) of the representative compounds (Example 13,14, and 17) of the present invention was examined by oral administration daily for 21 days in mice. The representative LD_{50} values obtained from the experiments were more than 500 mg/kg/day.

A dosage per day to a patient of the N^4-(substituted-oxycarbonyl)-5'-DFCRs of the present invention may be varied depending upon his weight and state to be remedied, but generally is in the range of 0.5 to 500 mg per 1 kg of weight, preferably about 2 to 200 mg. It should be noted that the compound of the invention can be expected to have 3–5 times higher activity than those of the compounds disclosed in U.S. Pat. No. 4,966,891 in humans, when taking into consideration of the data of C_{max} and AUC of 5'-DFUR after oral administration of the present compounds in monkeys. From the same reason, the compounds of the present invention can be expected to show sufficient activity at the 3–5 times lower dosage than those of the compounds of U.S. Pat. No. 4,966,891. The present invention can provide a pharmaceutical composition for treating tumors with high safety margin.

The following Examples are intended to illustrate the present invention in more detail, but are not intended to limit its scope in any manner.

Reference example: Preparation of starting material

Preparation of 2',3'-di-O-acetyl-5'-deoxy-5-fluorocytidine

(a) From 5'-deoxy-5-fluorocytidine

5'-Deoxy-5-fluorocytidine (50 mg) was dissolved in dry pyridine (1.3 ml). To the solution was added acetic anhydride (39 ml) with stirring at 0° C. The reaction mixture was stirred for 3 hours at 0° C. After removal of the solvent under reduced pressure, the residue was partitioned between ethyl

acetate and ice cooled water. The ethyl acetate layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane/methanol=9/1 as an eluent) followed by recrystallization from isopropanol to give 37 mg of 2',3'-di-O-acetyl-5'-deoxy-5-fluorocytidine; 191.5°–193° C., FAB-MS m/z 330 (MH^+).

(b) From 5-fluorocytosine and 1,2,3-tri-O-acetyl-5-deoxy-β-D-ribofuranose

A solution of sodium iodide (3.6 g) and chlorotrimethylsilane (794 ml) in dry acetonitrile (15 ml) was stirred with molecular sieves 4A (200 mg) at 0° C. for 5 minutes (colorless sodium chloride deposited during stirring). 1,2,3-Tri-O-acetyl-5-deoxy-β-D-ribofuranose (2.0 g) was added and the mixture was stirred at 0° C. for 30 min. Then, a solution of the trimethylsilylated 5-fluorocytosine, freshly prepared from 5-fluorocytosine (1.12 g), in dry acetonitrile (5 ml) was added at 0° C. and stirring was continued for 3 h at room temperature. The mixture was filtered, the filtrate was concentrated in vacuo, and the residue was partitioned between dichloromethane and saturated aq. sodium bicarbonate solution. The aqueous layer was extracted with CH_2Cl_2/MeOH (10:1). The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (15:1) as an eluent, followed by recrystallization from isopropanol to give 1.24 g of 2',3'-di-O-acetyl-5'-deoxy-5-fluorocytidine.

Example 1

Preparation of 2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine

To a solution of 2',3'-di-O-acetyl-5'-deoxy-5-fluorocytidine (2 g) in CH_2Cl_2 (15 ml) and dry pyridine (983 ml) was added dropwise n-propyl chloroformate (957 ml) with stirring and cooling on ice bath. After stirring for 30 min at room temperature, the mixture was evaporated to dryness under reduced pressure. The residue was partitioned between ether and saturated aqueous solution of sodium bicarbonate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered.

The filtrate was evaporated to give 2',3'-di-O-acetyl-5'-deoxy-5- fluoro-N^4-(propoxycarbonyl)cytidine (2.5 g) :EI-MS m/z 415(M^+); ^{1}H-NMR(d_6-DMSO) δ0.92 (3H, t, J=7.3 Hz), 1.37 (3H, d, J=6.3 Hz), 1.63 (2H, sex, J=7.3 Hz), 4.06–4.14 (3H, m), 5.11 (1H, t, J=6.3 Hz), 5.47 (1H, d.d., J=4.6 & 6.3 Hz), 5.81 (1H, d, J=4.6 Hz), 8.31 (1H, br. s), 10.63 (1H, br. s)

The following compounds were obtained according to a manner analogous to that of Example 1. The compound of Example 9 was prepared from the known 2',3'-di-O-benzoyl-5'-deoxy-5-fluorocytidine (U.S. Pat. No. 4,966,891) by the similar manner to that of Example 1.

Example No.	R^1	R^2	^{1}H-NMR (in solvent 1 or 2)	FAB-MS (m/z)
2	n-butyl	acetyl	δ(1): 0.87(3H, t, J=7.3Hz), 1.36(5H, m), 1.59(2H, m), 2.05(3H, s), 2.07(3H, s), 4.12(3H, m), 5.11(1H, br.t), 5.47(1H, br. t), 5.81(1H, d, J=4.3Hz), 8.34 (1H, br.s), 10.60(1H, br.s)	430(MH^+)
3	n-pentyl	acetyl	δ(1): 0.88(3H, t, J=7.3Hz), 1.31(5H, m), 1.36 (3H, d, J=6.3Hz), 1.61(1H, m), 2.06(3H, s), 2.07(3H, s), 4.07–4.14(3H, m), 5.11(1H, t, J=6.3Hz), 5.47(1H, d.d, J=6.3 & 4.6Hz), 5.80(1H, d, J=4.6Hz), 8.28(1H, br.s), 10.63(1H, br.s)	444(MH+)
4	n-hexyl	acetyl	δ(1): 0.87(3H, t, J=6.9Hz), 1.30(6H, m), 1.36(3H, d, J=6.3Hz), 1.59(2H, m), 2.06(3H, s), 2.07(3H, s), 4.07–4.14(3H, m), 5.11(1H, t, J=6.3Hz), 5.45(1H, d.d, J=6.3 & 4.6Hz), 5.80(1H, d, J=4.6Hz), 8.28(1H, br s), 10.63(1H, br.s)	458(MH+)
5	isopentyl	acetyl	δ(1): 0.90(6H, d, J=6.9Hz), 1.36(3H, d, J=6.3Hz), 1.51 (2H, q, J=6.9Hz), 1.68(1H, m), 2.06(3H, s), 2.07 (3H, s), 4.09–4.20(3H, m), 5.11(1H, t, J=6.3Hz), 5.46(1H, d.d, J=6.3 & 4.3Hz), 5.80(1H, d, J=4.3Hz), 8.28(1H, br.s), 10.63(1H, br.s)	444(MH+)
6	2-ethylbutyl	acetyl	δ(1): 0.87(6H, t, J=7.3Hz), 1.23–1.45(7H, m), 1.51(1H, m), 2.06(3H, s), 2.07(3H, s), 4.04 (2H, br.d), 4.12(1H, t, J=6.3Hz), 5.11(1H, t, J=6.3Hz), 5.46(1H, d.d., J=6.3 & 4.6Hz), 5.81 (d, J=4.6Hz), 8.32(1H, br.s), 10.61(1H, br.s)	458(MH+)
7	cyclohexyl-methyl	acetyl	δ(1): 1.00(2H, m), 1.11–1.29(4H, m), 1.36(3H, d, J=6.3Hz), 1.57–1.77(5H, m), 2.06(3H, s), 2.07 (3H, s), 3.92(2H, br.s), 4.12(1H, m), 5.11(1H, t, J=6.3Hz), 5.46(1H, d.d, J=6.3 & 4.0Hz), 5.81(1H, d, J=4.0Hz), 8.33(1H, br.s), 10.61(1H, br.s)	470(MH+)
8	phenethyl	acetyl	δ(1): 1.36(3H, d, J=6.3Hz), 2.06(3H, s), 2.07 (3H, s), 2.94(2H, t, J=6.8Hz), 4.12(1H, m), 4.32 (2H, br.t), 5.11(1H, t, J=6.3Hz), 5.46(1H, d.d, J=6.3 & 4.3Hz), 5.81(1H, d, J=4.3Hz), 7.16–7.37 (5H, m), 8.32(1H, br.s), 10.67(1H, br.s)	478(MH+)
9	n-butyl	benzoyl	δ(2): 0.95(3H, t, J=7.3Hz), 1.42(2H, m) 1.58 (3H, d, J=6.3Hz), 1.68(2H, m), 4.16(2H, br.s), 4.52(1H, d.q, J=5.8 & 6.3Hz), 5.40(1H, t, J=5.8Hz) 5.65(1H, d.d, J=4.6 & 5.8Hz), 6.16(1H, d, J=4.6Hz), 7.35–7.98(11H, m), 11.9(1H, br.s)	554(MH+)

NMR: solvent 1 = d_6-DMSO, Solvent 2 = $CDCl_3$

Example 10

Preparation of 5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine

To a solution of 2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine (2.5 g) in CH_2Cl_2 (17 ml) was added dropwise 1N NaOH (17 ml) with stirring and cooling with ice bath. After stirring for 1 hr at 0° C., MeOH (0.9 ml) was added to the mixture. And pH of the reaction mixture was adjusted to 6 by the addition of concentrated HCl and partitioned. The aqueous layer was extracted with a mixed solvent of CH_2Cl_2/MeOH(95/5) successively (40 ml×10). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solution was evaporated, and the residue was crystallized from ethyl acetate to give 5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine as colorless crystals (1.6 g, y. 79.8%): mp. 125°–126.5° C.; EI-MS m/z 331 (M^+).

The following compounds were obtained according to a manner analogous to that of Example 10.

Example No.	R^1	R^2	Melting point (°C.)	Recrystallization solvent	FAB-MS m/z
11	n-butyl	H	119–120	AcOEt	346(MH^+)
12	n-pentyl	H	110–121	AcOEt	EI 359(M^+)
13	n-hexyl	H	114–116	AcOEt	EI 373(M^+)
14	isopentyl	H	119–120	AcOEt	360(MH^+)
15	2-ethylbutyl	H	amorphous*	—	374(MH^+)
16	cyclohexyl-methyl	H	126–127	AcOEt	386(MH^+)
17	phenethyl	H	144–145	AcOEt—MeOH	394(MH^+)
18	allyl	H	118.5–120	AcOEt	330(MH^+)

*^{1}H-NMR(d_6-DMSO) of Example 15: δ 0.87(6H, t, J=7Hz), 1.25–1.45(7H, m), 1.53(1H, m), 3.68(1H, q., J=6 Hz), 3.89(1H, br. t, J=6Hz), 4.02(2H, d, J=6Hz), 4.10(1H, m), 5.05(1H, d, J=6Hz), 5.4(1H, d, J=6Hz), 5.67(1H, d, J=3Hz), 8.00(1H, br. s), 10.55 & 11.60 (total 1H, br. s each).

Example 19

Preparation of N^4-(cyclohexyloxycarbonyl)-5'-deoxy-5-fluorocytidine

5'-Deoxy-5-fluorocytidine (2.5 g) was dissolved in dry pyridine (20 ml). To the mixture, trimethylsilyl chloride (3.4 ml) was added dropwise at 0° C., and stirred for 30 min at room temperature. To the reaction mixture, cyclohexyl chloroformate (2.0 ml) was added in one portion at 0° C. After stirring of the mixture for 1 hour at room temperature, pyridine was evaporated under reduced pressure. The residue was then partitioned between saturated aqueous $NaHCO_3$ and ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. To the residue were added citric acid (2.0 g) and methanol (50 ml). The mixture was stirred at room temperature overnight. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2/MeOH (95:5) and neutralized by aqueous NaOH. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (20:1) as an eluent, followed by recrystallization from ethyl acetate to give N^4-(cyclohexyloxycarbonyl)-5'-deoxy-5-fluorocytidine (3.47 g:92% yield):mp. 134°–136° C., FAB-MS m/z 372 (MH^+).

The following compounds were obtained according to a manner analogous to that of Example 19.

Example No.	R^1	R^2	Melting point (°C.)	Recrystallization solvent	FAB-MS m/z
20	2-cyclohexyl-ethyl	H	128–129.5	AcOEt	400(MH^+)
21	3-cyclohexyl-propyl	H	amorphous*	—	414(MH^+)
22	3-phenyl-propyl	H	120–121	AcOEt	408(MH^+)
23	2-methoxy-ethyl	H	amorphous**	—	348(MH^+)
24	isobutyl	H	132–134	AcOEt	346(MH^+)
25	2-propylpentyl	H	116–118	AcOEt	402(MH^+)
26	2-ethylhexyl	H	amorphous***	—	402(MH^+)

-continued

Example No.	R^1	R^2	Melting point (°C.)	Recrystallization solvent	FAB-MS m/z
27	n-heptyl	H	115.5–117.5	AcOEt	388(MH^+)

*^{1}H-NMR(d_6-DMSO) of Example 21:
δ 0.78–0.93(2H, m), 1.15–1.27(6H, m), 1.31(3H, d, J=7Hz), 1.59–1.75(7H, m), 3.68(1H, q, J=6Hz), 3.89(1H, br. t, J=6Hz), 4.01–4.14(3H, m), 5.04(1H, d, J=6Hz), 5.40(1H, d, J=6Hz), 5.67(1H, d, J=2Hz), 8.00(1H, br. s), 10.03 & 10.53(total 1H, br. s each).
**^{1}H-NMR(d_6-DMSO) of Example 23:
δ 1.31(3H, d, J=5.9Hz), 3.28(3H, s), 3.56(2H, br. t), 3.69(1H, t, J=6Hz), 3.89(1H, m), 4.06(1H, m), 4.22(2H, br. t), 5.05(1H, d, J=6Hz), 5.40(1H, br. s), 5.67(1H, d, J=3Hz), 8.06(1H, br. s), 10.65(1H, br. s).
***^{1}H-NMR(d_6-DMSO) of Example 26:
δ 0.85–0.88(6H, m), 1.27–1.38(11H, m), 1.57(1H, br. d, J=6Hz), 3.68(1H, q, J=6Hz), 3.89–4.02(4H, m), 5.05(1H, br. s), 5.41(1H, br. s), 5.67(1H, d, J=3Hz), 8.06(1H, br. s), 10.52(1H, br. s).

Example 28

Preparation of 5'-deoxy-5-fluoro-N^4-(neopentyloxycarbonyl)cytidine

5'-Deoxy-2',3'-di-O-acetyl-5-fluorocytidine (1.5 g) and dry pyridine (0.74 ml) were dissolved in dry dichloromethane (15 ml). To the mixture, toluene solution of neopentyl chloroformate (3 eq.) was added dropwise at 0° C., and stirred at room temperature for 1 hour. After the solvent was removed under reduced pressure, the residue

was partitioned between ether and saturated aqueous solution of sodium carbonate. The organic layer was successively washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude 2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4(neopentyloxycarbonyl)cytidine as pale yellow oil. This crude product was dissolved in ethanol (15 ml) and cooled on ice-bath. Then 1N aqueous sodium hydroxide solution was added dropwise while maintaining the temperature below 15° C. After the addition was completed, the reaction mixture was neutralized with concentrated. hydrochloric acid at 0° C. The solution was concentrated under reduced pressure, and the concentrate was partitioned between water and a mixed solution of CH_2Cl_2/MeOH (95:5). The aqueous layer was back-extracted with CH_2Cl_2/MeOH (95:5) ten times (20 ml each). All organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2/MeOH (20:1) as an eluent to give 5'-deoxy-5-fluoro-N^4-(neopentyloxycarbonyl)cytidine (1.37 g: 84% yield) as amorphous powder: FAB-MS m/z 360 (MH^+); ^{1}H-NMR (d_6-DMSO) δ0.93 (9H, s), 1.31 (3H, d,J=6.3 Hz), 3.68 (1H,q,J=5.9 Hz), 3.81 (2H, br. s), 3.87–3.92 (1H, m), 4.04–4.09 (1H, m), 5.05 (1H,d, J=5.9 Hz), 5.41 (1H, br. d, J=5.3 Hz), 5.67 (1H,dd,J=1.3, 3.6 Hz), 8.04 (1H, br. s), 10.53 (–1H, br. s).

Example 29

Preparation of 5'-Deoxy-N^4-[(3,3-dimethylbutoxy)carbonyl]-5-fluorocytidine

5'-Deoxy-N^4-[(3,3-dimethylbutoxy)carbonyl]-5-fluorocytidine was obtained according to a manner analogous to that of Example 28 except that 3,3-dimethylbutyl chloroformate was used as the acylating agent:amorphous powder (71% yield); FAB-MS m/z 374 (MH^+); ^{1}H-NMR (d_6-DMSO) δ0.93 (9H, s), 1.31 (3H,d,J=6.3 Hz), 1.55 (2H, t,J=7.3 Hz), 3.68 (1H,q,J=5.9 Hz), 3.84–3.93 (1H, m), 4.03–4.09 (1H, m), 4.15 (2H,t,J= 7.3 Hz), 5.05 (1H,d,J=5.9 Hz), 5.40 (1H, br, d,J=5.3 Hz), 5.67 (1H,dd,J=1.3, 4.0 Hz), 8.00 (1H, br. s), 10.53 (–1H, br. s).

The following examples illustrate pharmaceutical preparations containing a compound provided by the present invention.

Example A

Interlocking gelatin capsules each containing the following ingredients were manufactured in a manner known per se:

N^4-(Butoxycarbonyl)-5'-deoxy-5-fluorocytidine	100 mg
Corn starch	20 mg
Titanium dioxide	385 mg
Magnesium stearate	5 mg
Film	20 mg
PEG 6000	3 mg
Talc	10 mg
	543 mg

Example B

Tablets each containing the following ingredients were manufactured in a manner known per se:

N^4-(Butoxycarbonyl)-5'-deoxy-5-fluorocytidine	100 mg
Lactose	25 mg
Corn starch	20.2 mg
Hydroxypropylmethyl cellulose	4 mg
Magnesium stearate	0.8 mg
Film	10 mg
PEG 6000	1.5 mg
Talc	4.5 mg
	166 mg

Example C

Dry parenteral dosage forms were manufactured in a manner known per se:

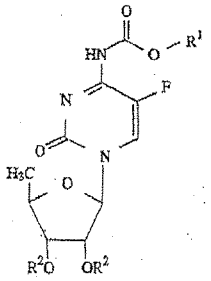
(1) A total 5 g of N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine was dissolved in 75 ml of distilled water, the solution was subjected to a bacteriological filtration, and then divided aseptically into 10 sterile vials. The solution was then freeze-dried to yield 500 mg of sterile dry solid per vial.

(2) Clean N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine in the amount of 500 mg per vial or ampoule was sealed in the receptacle and heat-sterilized.

The above dry dosage forms were reconstituted before use by adding a suitable sterile aqueous solvent such as water for injection or isotonic sodium chloride or 5% dextrose for parenteral administration.

We claim:

1. A compound of formula (I),



(I)

wherein R^1 is a saturated straight or branched hydrocarbon radical wherein the number of carbon atoms in the longest straight chain of this hydrocarbon radical ranges from three to seven, or is a radical of the formula $—(CH_2)n—^Y$ wherein Y is a cyclohexyl radical, a C_1–C_4 alkoxy radical or a phenyl radical and wherein when Y is a cyclohexyl radical n is an integer from 0 to 4, and when Y is C_1–C_4 alkoxy radical or a phenyl radical n is an integer from 2 to 4, and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

or a hydrate or solvate thereof.

2. The compounds according to claim 1, wherein R^1 is selected from the group consisting of n-propyl, 1-isopropyl-2-methylpropyl, 1,1,2-trimethylpropyl, n-butyl, isobutyl, 2-ethylbutyl, 3,3-dimethylbutyl, n-pentyl, isopentyl, neopentyl, 2-propylpentyl, n-hexyl, 2-ethylhexyl, n-hetpyl, cyclohexyl, cyclohexylbutyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, 4-methoxybutyl, 4-ethoxybutyl, phenethyl, 3-phenyl-propyl and 4-phenylbutyl.

3. The compounds according to claim 1, selected from a group consisting of:

5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(hexyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(isopentyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-(neopentyloxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-[(1,1,2-trimethylpropoxy)carbonyl]cytidine,

5'-deoxy-N^4-[(3,3-dimethylbutoxy)carbonyl]-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-[(1-isopropyl-2-methylpropoxy-)carbonyl]cytidine,

5'-deoxy-N^4-[(2-ethylbutyl)oxycarbonyl]-5-fluorocytidine,

N^4-[(cyclohexylmethoxy)carbonyl]-5'-deoxy-5-fluorocytidine,

5'-deoxy-5-fluoro-N^4-[(2-phenylethoxy)carbonyl]cytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine,

2',3'-di-O-acetyl-N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine,

2',3'-di-O-benzoyl-N^4-(butoxycarbonyl)-5 '-deoxy-5-fluorocytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(pentyloxycarbonyl)cytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(isopentyloxycarbonyl)cytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-(hexyloxycarbonyl)cytidine,

2',3'-di-O-acetyl-5'-deoxy-N^4-[(2-ethylbutyl)oxycarbonyl]-5-fluorocytidine,

2',3'-di-O-acetyl-N^4-[(cyclohexylmethoxy)carbonyl]-5'-deoxy-5-fluorocytidine,

2',3'-di-O-acetyl-5'-deoxy-5-fluoro-N^4-[(2-phenylethoxy-)carbonyl]cytidine,

5'-deoxy-5-fluoro-N^4-(isobutoxycarbonyl)cytidine,

5'-deoxy-5-fluoro-N^4-[(2-propylpentyl)oxycarbonyl]cytidine,

5'-deoxy-N^4-[(2-ethylhexyl)oxycarbonyl]-5'-fluorocytidine,

5'-deoxy-5-fluoro-N^4-(heptyloxycarbonyl)cytidine,

N^4-[(2-cyclohexylethoxy)carbonyl]-5'-deoxy-5-fluorocytidine,

N^4-[(3-cyclohexylpropyl)oxycarbonyl]-5'-deoxy-5-fluorocytidine,

N^4-(cyclohexyloxycarbonyl)-5'-deoxy-5-fluorocytidine,

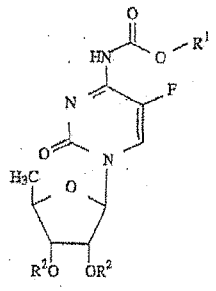
5'-deoxy-5-fluoro-N^4-[(3-phenylpropyl)oxycarbonyl]cytidine,

5'-deoxy-5-fluoro-N^4-[(2-methoxyethoxy)carbonyl]cytidine,

N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine and

5'-deoxy-5-fluoro-N^4-(pentyloxycarbonyl)cytidine.

4. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of formula (I)

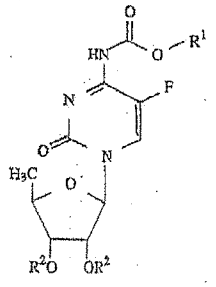


(I)

wherein R^1 is a saturated straight or branched hydrocarbon radical wherein the number of carbon atoms in the longest straight chain of the hydrocarbon radical ranges from three to seven, or is a radical of the formula $-(CH_2)_n-Y$ wherein Y is a cyclohexyl radical, a C_1–C_4 alkoxy radical or a phenyl radical and wherein when Y is a cyclohexyl radical n is an integer from 0 to 4 and when Y is a C_1–C_4 alkoxy radical or a phenyl radical n is an integer from 2 to 4, and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

or a hydrate or solvate thereof, and an inert carrier.

5. A method of treating tumors comprising administering to a host in need of such treatment an effective amount of a compound of formula (I)



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or a hydrate or solvate thereof.

6. The compound according to claim 1, 5'-deoxy-5-fluoro-N^4- (pentyloxycarbonyl)cytidine.

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