Our Ref: 488860

P/00/001
Section 29

AUSTRALIA

Patents Act 1990

PATENT REQUEST : STANDARD PATENT

I/We, being the person/s identified below as the Applicant, request the grant of a patent to the person/s indicated below as the Nominated Person/s, for an invention described in the accompanying standard complete specification.

Full application details follow.

[71] [70] Applicant/s and Nominated Person/s:
F Hoffmann-La Roche AG,
of 124 Grenzacherstrasse, CH-4002 BASLE, SWITZERLAND

[54] Invention Title:
N-Oxycarbonyl substituted 5'-deoxy-5-fluorcytidines

[72] Name/s of actual inventor/s: (optional)

[74] Address for service in Australia:
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BASIC CONVENTION APPLICATION/S DETAILS:

[31] Appln No.:	[33] Country:	Code:	[32] Date:
92121538.0	EUROPE	EP	18 December 1992

Basic Applicant/s: F Hoffmann-La Roche Ag

DATED this TWELFTH day of NOVEMBER 1993

F Hoffmann-La Roche AG
By Patent Attorneys
DAVIES COLLISON CAVE

Peter Stearne

Dr. PETER STEARNE, FIPAA

Fee: $ 195.00

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AUSTRALIA

Patents Act 1990

PATENT REQUEST : STANDARD PATENT / PATENT OF ADDITION

We, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow:

[71/70] Applicant/Nominated Person:

F Hoffmann-La Roche AG

Address:

124 Grenzacherstrasse, CH-4002 Basle, Switzerland.

[54] Invention Title:

N-Oxycarbonyl substituted 5'-deoxy-5-fluorcytidines

[72] Name(s) of actual inventor(s):

Motohiro Arasaki, Hideo Ishitsuka, Isami Kuruma, Masanori Miwa, Chikako Murasaki, Nobuo Shimma and Isao Umeda

[74] Address for service in Australia:

DAVIES COLLISON CAVE, Patent Attorneys, of Level 10, 10 Barrack Street, Sydney, 2000, Australia. Attorney Code: CA

BASIC CONVENTION APPLICATION(S) DETAILS:

[31] Application No.	[33] Country	Code	[32] Date
92121538.0	Europe (designating Switzerland)	CH	18 December 1992

A member of the firm of DAVIES COLLISON CAVE
for and on behalf of the applicant

AUSTRALIAN PATENT OFFICE 13

25 June, 1996

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

We, **F HOFFMANN-LA ROCHE AG**, of 124 Grenzacherstrasse, CH-4002 Basle, Switzerland, the Applicant in respect of Application No. 50690/93 state the following:

1 F Hoffmann-La Roche AG is the Nominated Person in respect of the application.

2. The actual inventors of the invention, the subject of the application, are Motohiro Arasaki, Hideo Ishitsuka, Isami Kuruma, Masanori Miwa, Chikako Murasaki, Nobuo Shimma and Isao Umeda.

3. The Nominated Person, F Hoffmann-La Roche AG, is entitled to the grant of a patent in respect of the application because the said Nominated Person derived title to the invention from the actual inventors by assignment.

4. The Nominated Person is entitled to claim priority from the basic application listed on the patent request form because (i) the Nominated Person is the Applicant in respect of the basic application; and (ii) the basic application was the first application made in a Convention country in respect of the invention the subject of the application.

Dated this 25th day of June, 1996.

F HOFFMANN-LA ROCHE AG
By Its Patent Attorneys
DAVIES COLLISON CAVE

JAMES G SIELY, FIPAA

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-50690/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 671491

(54) Title
N-OXYCARBONYL SUBSTITUTED 5'-DEOXY-5-FLUORCYTIDINES

International Patent Classification(s)
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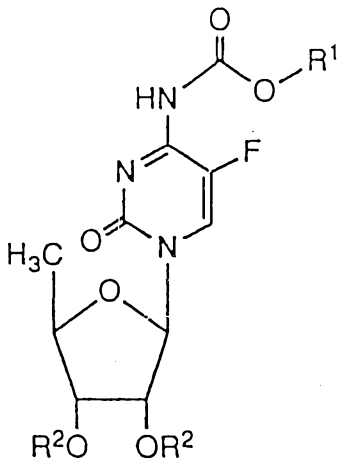
(56) Prior Art Documents
AU 619220 25168/88 C07H 19/67

It was found these compounds have significantly improved pharmacokinetic profiles over prior art compounds.

CLAIM

1. Compounds represented by the general 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 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

.../2

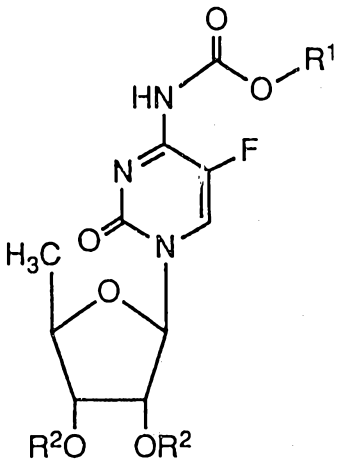
integer from 2 to 4, when Y is a lower alkoxy radical having 1 to 4 carbon atom(s) or a phenyl radical], and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

as well as hydrates or solvates of the compounds of the general formula (I).

RAN 4060/166

The present invention relates to N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine derivatives, and a pharmaceutical composition containing the same for treating tumors.

More particularly, the present invention relates to N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine derivatives represented by the general 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 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 1 to 4 carbon atom(s) or a phenyl radical], and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

as well as hydrates or solvates of the compounds of the general formula (I), and a pharmaceutical composition containing the same with excellent pharmacokinetic profiles for treating tumors with high safety margin.

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 and they

cause intestinal toxicities and immunosuppressive toxicities, which are their major and dose limiting toxicities.

USP 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. During intensive studies on the pharmacokinetic profiles of the precursors of 5-FU, particularly of N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine derivatives, the inventors found 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. The further studies based on the above findings enabled the inventors of the present invention to identify that the specific N^4-(substituted-oxycarbonyl)-5'-deoxy-5-fluorocytidine derivatives (hereinafter referred to as N^4-(substituted-oxycarbonyl)-5'-DFCR) represented by the above mentioned general formula (I) have selectively improved pharmacokinetic profiles in monkeys, viz. 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, and thus completed the present invention.

The respective radicals of the general formula (I) which are defined above are explained in more detail as follows;

Explanation of R^1:

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 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 1 to 4 carbon atom(s) or a phenyl radical].

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 signifies 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 signifies 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.

In the most preferred embodiment of the compounds in accordance with the present invention, R^1 signifies n-propyl, n-butyl, n-pentyl, isopentyl, neopentyl, 3,3-dimethylbutyl, n-hexyl, 2-ethylbutyl, phenylethyl, and cyclohexylmethyl.

Explanation of R^2:

R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological condition.

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

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

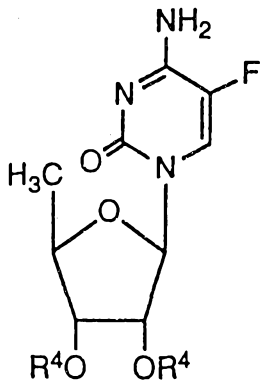
5'-deoxy-5-fluoro-N^4-(propoxycarbonyl)cytidine,
5'-deoxy-5-fluoro-N^4-(isopentyloxycarbonyl)cytidine,
5'-deoxy-5-fluoro-N^4-(hexyloxycarbonyl)cytidine,
5'-deoxy-N^4-[(2-ethylbutyl)oxycarbonyl]-5-fluorocytidine,
5'-deoxy-5-fluoro-N^4-(neopentyloxycarbonyl)cytidine,
5'-deoxy-N^4-[(3,3-dimethylbutoxy)carbonyl]-5-fluorocytidine,
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.

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



(II)

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

with a compound represented by the general 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 represented by the above general 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 USP 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 the literature [*Synthesis*, 748 (1981)].

The reaction of the compound of the above general formula (II) with the compound of the above general 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 USP 4,966,891], e.g. by basic or acidic hydrolysis.

The compounds of the above general 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. Solvates with pharmaceutically acceptable solvents such as ethanol can be obtained during, for example, crystallization.

N^4-(Substituted-oxycarobonyl)-5'-DFCR derivatives represented by the general formula (I) as well as hydrates or solvates of the compounds of the general formula (I) prepared by the present invention 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 present invention further relates to a pharmaceutical composition, particularly for the treatment of tumors characterized by containing a compound of the above general formula (I).

The N^4-(substituted-oxycarbonyl)-5'-DFCRs of the present invention can be administered orally or non-orally to human beings by various conventional administration methods. Moreover, the N^4-(substituted-oxycarbonyl)-5'-DFCRs according to the present 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 (e.g. as tablets, dragees, enteric coating tablets, granulars, enteric coating granulars, suppositories, capsules or enteric capsules) in a semi-solid form (e.g. as salves) or in a liquid form (e.g. 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.

Susceptibility to acylamidase of the N^4-(substituted-oxycarbonyl)-5'-DFCRs of the present invention and their pharmacokinetic profiles in the monkey are shown as follows:

1. Susceptibility to human and monkey acylamidases

The N^4-(substituted-oxycarbonyl)-5'-DFCRs of the present 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 provided in the present invention 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 the present invention 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 provided in the present 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 present invention are shown as follows:

3. Antitumor testing against human colon cancer xenograft CXF280

CXF280 tumor (about 2 x 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 present 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 x 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

Compound (Example No.)	Dose x 21 (mmol/kg/day)	% Growth inhibition	Fecal observation *
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 x 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 USP 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 said U.S. Patent. 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 resudie 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 min (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 resudie 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) δ 0.92 (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 (R^1 and R^2 are the same with those in the general formula (I)). The compound of Example was prepared from the known 2',3'-di-O-benzoyl-5'-deoxy-5-fluorocytidine 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=6.3 Hz), 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^+)

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

Example No.	R^1	R^2	^{1}H-NMR (in solvent 1 or 2)	FAB-MS (m/z)
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 x 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 (R^1 and R^2 are the same with those in the general formula (I)).

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=7 Hz), 1.25-1.45 (7H, m), 1.53 (1H, m), 3.68 (1H, q., J=6 Hz), 3.89 (1H, br. t, J=6 Hz), 4.02 (2H, d, J=6 Hz), 4.10 (1H, m), 5.05 (1H, d, J=6 Hz), 5.4 (1H, d, J=6 Hz), 5.67 (1H, d, J=3 Hz), 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 (3.47g : 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 (R^1 and R^2 are the same with those in the general formula (I)).

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-propylethyl	H	116-118	AcOEt	402 (MH^+)
26	2-ethylhexyl	H	amorphous***	-	402 (MH^+)
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=7 Hz), 1.59-1.75 (7H, m), 3.68 (1H, q, J=6 Hz), 3.89 (1H, br. t, J=6Hz), 4.01-4.14 (3H, m), 5.04 (1H, d, J=6Hz), 5.40 (1H, d, J=6 Hz), 5.67 (1H, d, J=2 Hz), 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=5.9 Hz), 3.28 (3H, s), 3.56 (2H, br. t), 3.69 (1H, t, J=6 Hz), 3.89 (1H, m), 4.06 (1H, m), 4.22 (2H, br. t), 5.05 (1H, d, J=6 Hz), 5.40 (1H, br. s), 5.67 (1H, d, J=3 Hz), 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=6 Hz), 3.68 (1H, q, J=6 Hz), 3.89-4.02 (4H, m), 5.05 (1H, br. s), 5.41(1H, br. s), 5.67 (1H, d, J=3 Hz), 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 hr. 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 conc. 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) δ 0.93 (9H, s), 1.31 (3H, d,J=6.3Hz), 3.68 (1H,q,J=5.9Hz), 3.81 (2H, br. s), 3.87-3.92 (1H, m), 4.04-4.09 (1H, m), 5.05 (1H,d,J=5.9Hz), 5.41 (1H, br. d, J=5.3Hz), 5.67 (1H,dd,J=1.3,3.6Hz), 8.04 (1H, br. s), 10.53 (~1H, br. s).

Example 29

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) δ 0.93 (9H, s), 1.31 (3H,d,J=6.3Hz), 1.55 (2H,t,J=7.3Hz), 3.68 (1H,q,J=5.9Hz), 3.84-3.93 (1H, m), 4.03-4.09 (1H, m), 4.15 (2H,t,J=7.3Hz), 5.05 (1H,d,J=5.9Hz), 5.40 (1H, br, d,J=5.3Hz), 5.67 (1H,dd,J=1.3,4.0Hz), 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*:

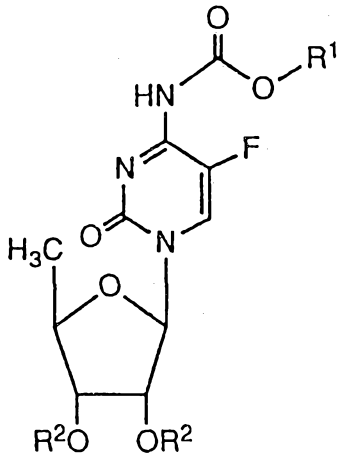
(1) A total 5 g of N^4-(butoxycarbonyl)-5'-deoxy-5-fluorocytidine was dissolved in 75 ml of distilled water, the solution was subjected to a bacteriological filtration, and then divided aseptically into 10 sterile vials. The solution was then freeze-dried to yield 500 mg of sterile dry solid per vial.

(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 suitalble sterile aqueous solvent such as water for injection or isotonic sodium chloride or 5% dextrose for parenteral administration.

The Claims defining the invention are as follows:

1. Compounds represented by the general 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 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 1 to 4 carbon atom(s) or a phenyl radical], and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,
as well as hydrates or solvates of the compounds of the general formula (I).

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-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, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 3-cyclohexylpropyl, 4-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,

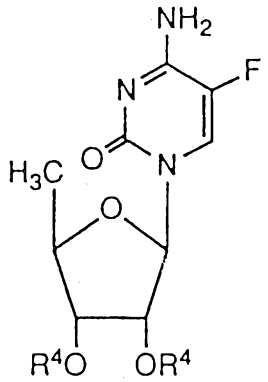
N^4-(cyclohexyloxycarbonyl)-5'-deoxy-5-fluorocytidine,

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

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

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

4. A process for producing the compounds according to claim 1, which comprises reacting a compound represented by the general formula (II),



(II)

wherein R^4 is a hydroxy-protecting radical,

with a compound represented by the general formula (III)

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

wherein R^1 is as defined in claim 1,

and, if necessary, removing the protecting radicals.

5. A pharmaceutical composition, particularly for the treatment of tumors characterized by containing a compound of the general formula (I), according to claim 1, or a hydrate or solvate of the said compound of the general formula (I), as an active ingredient, together with a compatible pharmaceutical carrier material.

6. A method for the treatment of tumors wherein there is administered, to a subject in need of such treatment, a compound according to any one of claims 1 to 3, or a composition according to claim 5.

7. Compounds according to claim 1 whenever prepared by the process of claim 4.

8. A compound according to claim 1 substantially as herein described with reference to any one of the foregoing examples thereof.

9. A process according to claim 4 substantially as herein described with reference to any one of the foregoing examples thereof.

10. A composition according to claim 5 substantially as herein described with reference to any one of the foregoing examples thereof.

DATED this 25th day of June, 1996.

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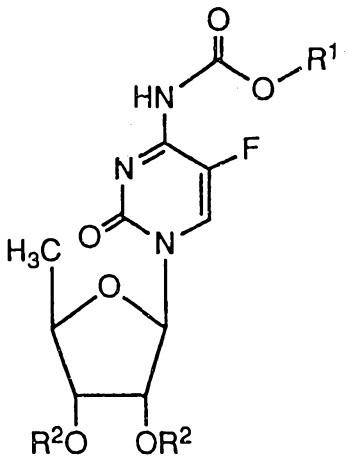
By Its Patent Attorneys
DAVIES COLLISON CAVE

Abstract

Compounds represented by the general 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 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 1 to 4 carbon atom(s) or a phenyl radical], and R^2 is a hydrogen atom or a radical easily hydrolyzable under physiological conditions,

as well as hydrates or solvates of the compounds of the general formula (I), can be utilized in the treatment of tumors, They can be prepared by reacting a compound of formula R^1-OCOCl with a N^4-unsubstituted 5'-deoxy-5-fluorocytidine of the above formula I, wherein R^2 would stand for protecting groups, and if necessary removing the protecting groups.