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Description

While the treatment of cancer was once considered impossible, great strides have been made during the past ten years in controlling the ravages of this often fatal disease. Several drugs which contribute to the increasing rate of survival are now routinely used clinically. The most commonly employed antitumor agents include methotrexate, doxorubicin and the vinca alkaloids such as vincristine. However, research continues to develop more effective compounds with greater safety for subjects under treatment. This invention provides valuable improvements in the treatment of tumors.


The present invention provides a method of treating susceptible neoplasms in mammals comprising administering to said mammal a pharmaceutically effective amount of a compound of formula (I):

\[
\text{(I)}
\]

in which:

- \( R^1 \) is hydrogen, \( C_1-C_4 \) alkyl or

\[
\begin{array}{c}
\text{O} \\
\text{C-R}^5;
\end{array}
\]

- \( R^2 \) is a base defined by one of the formulae

\[
\begin{align*}
\text{NHR}^3 \\
\text{HN1} \\
\text{HN1} \\
\text{HN1} \\
\text{HN1} \\
\text{HN1}
\end{align*}
\]

- \( X \) is \( N \) or \( C-R^4 \);
- \( R^3 \) is hydrogen, \( C_1-C_4 \) alkyl or
R\(^5\) is hydrogen, C\(_1\)-C\(_4\) alkyl, amino, bromo, fluoro, chloro or iodo; each R\(^2\) independently is hydrogen or C\(_1\)-C\(_3\) alkyl; or a pharmaceutically-acceptable salt thereof.

Thus, the present invention provides for the use of a compound of formula (I) for the manufacture of a medicament for the treatment of susceptible neoplasms.

The present invention also provides a novel compound of formula (II):

\[
\begin{align*}
\text{(II)}
\end{align*}
\]

in which:
- R\(^6\) is hydrogen or C\(_1\)-C\(_4\) alkyl;
- R\(^7\) is a pyrimidine or purine base of one of the formulae

\[
\begin{align*}
\text{Q is N, C-}(C_2-C_4 \text{ alkyl}) \text{ or C-amino} \\
X \text{ is N or C-R}^6; \\
R^6 \text{ is hydrogen or C}_1-C_4 \text{ alkyl;} \\
R^7 \text{ is hydrogen, C}_1-C_4 \text{ alkyl, amino, bromo, fluoro, chloro and iodo; or a pharmaceutically-acceptable salt thereof; with the proviso that R}^6 \text{ and R}^7, \text{ both may be hydrogen only when X is N, and further provided the compound is not} \\
1-(2-\text{amino-6-oxo-1H,9H-purin-9-yl})-2-\text{deoxy-2,2-difluoropyrrole or} \\
1-(6-\text{amino-9H-purin-9-yl})-2-\text{deoxy-2,2-difluoropyrrole.}
\end{align*}
\]
The present invention further provides a compound of formula (III):

in which:
R⁸ is hydrogen or C₁⁻C₄ alkyl;
R⁹ is

or a pharmaceutically-acceptable salt thereof.

Further, there is provided a process for preparing a compound of formula (II) or (III), as defined above, which comprises:
(a) coupling a pyrimidine base of the formula R⁷H, or a protected derivative thereof, with a carbohydrate of formula IV, or a protected derivative thereof:

in which the R⁷H pyrimidine base and R⁹ are as defined above and Leav is a leaving group, and if desired, removing any protecting group present to produce the pyrimidine base product; and
(b) if a formula (III) or formula (II) compound in which the base is a purine is desired, reacting with ammonia a corresponding purine nucleoside compound in which a C-2 and/or C-6 substituent of the purine portion of the compound is halogen, and, if desired, alkylating the product.

The present invention also provides pharmaceutical formulations useful for treating susceptible neoplasms in mammals comprising a compound of formulae II or III in combination with a suitable pharmaceutically acceptable carrier, diluent or excipient thereof.

Further, there is provided a compound of formula (II) or (III) for use in the chemotherapy of a mammal.

The compounds employed in the present invention are preferably prepared by reacting a D-glyceraldehyde ketone with a C₁⁻C₅ alkyl bromodifluoracetate to afford an alkyl 3-dioxolanyl-2,2-difluoro-3-hydroxypropionate. The hydroxypropionate is hydrolyzed to a lactone which is protected and reduced to afford a 2-desoxy-2,2-difluororibose or xylose derivative. The hydroxy group of this compound is provided with a leaving group, and the resulting carbohydrate is coupled with an appropriate base. The resulting protected nucleoside is finally deprotected to provide the desired compound. The overall reaction scheme is
illustrated as follows:

wherein \( R^{10} \) and \( R^{11} \) independently are \( C_1-C_3 \) alkyl, "Prot" is a hydroxy protecting group and "Leav" is a leaving group.

It generally is desirable to convert free hydroxy groups to protected hydroxy groups during coupling of the 2-desoxy-2,2-difluorocarbohydrate to a base. The protecting groups are those commonly used in synthetic organic chemistry. Chemists are accustomed to choosing groups which can be placed efficiently on hydroxy groups, and which can be removed easily when the reaction is complete. Suitable groups may be those described in standard textbooks, such as Chapter 3 of Protective Groups in Organic Chemistry, McOmie, Ed., Plenum Press, New York (1973); and Chapter 2 of Protective Groups in Organic Synthesis, Greene, John Wiley & Sons, New York (1981).

Hydroxy-protecting groups commonly employed include formyl,
2-chloroacetyl, benzyl, diphenylmethyl, triphenylmethyl, 4-nitrobenzyl, phenoxy carbonyl, C1-C4 alkyl such as t-butyl, methoxy m ethyl, tetrahydropryran, allyl, tetrahydrothienyl, 2-methoxy ethoxy methyl, methoxyacetol, phenoxy acetyl, isobutyryl, ethoxy carbonyl, and benzoxycarbonyl. Silyl hydroxy protecting groups are particularly convenient because most are cleaved easily by contact with water or an alcohol. Such groups may include especially trimethylsilyl, as well as isopropyl dimethylsilyl, methyldiisopropylsilyl, or trisopropylsilyl. The t-butyldimethylsilyl group is a special case and is preferred as the protecting group in this synthesis; it is more difficult to cleave, requiring a reagent such as a hydrohalic acid to remove it from the hydroxy groups.

Ribose or xylose has a hydroxy group at the 1-position of its ring. In order to react the carbohydrate with the base, to form the compounds employed in this invention, a leaving group must be placed at the 1-position. The leaving groups are those typically used in organic synthesis. The preferred leaving groups are sulfonates, of which the most preferred is methanesulfonate. Other typical leaving groups such as toluenesulfonate, ethanesulfonate, isopropanesulfonate, 4-methoxybenzenesulfonate, 4-nitrobenzenesulfonate, 2-chlorobenzenesulfonate, chloro and bromo also may be used.

The carbohydrates employed in the synthesis of the compounds employed in the present invention are prepared by reacting a D-glyceraldehyde ketone of the formula

\[
\begin{align*}
R^{10} & \quad \text{O} \\
R^{11} & \quad \text{CHO}
\end{align*}
\]

wherein \( R^{10} \) and \( R^{11} \) are as defined above with a C1-C4 alkyl bromodifluoroacetate, preferably the ethyl ester.

The preferred glyceraldehyde ketone is the acetone in which \( R^{10} \) and \( R^{11} \) are both methyl (see Fischer and Baer, Helv. Chim. Acta, 17, 622 (1934)). Ethyl bromodifluoroacetate was prepared first by Morel and Dawans, Tet., 33, 1445 (1977). The reaction of the ketone and the haloacetate is carried out in the presence of an activated metal such as magnesium or preferably zinc. Activation is obtained most easily by applying ultrasonic energy to the reaction mixture. Activation by that means compensates for the presence of a small amount of water in the reaction mixture, avoiding the necessity to maintain anhydrous conditions, and also avoids the necessity to prepare and carefully store activated metals. However, if desired, the metal may be activated by the customary methods known in the art. Approximately an equimolar amount of metal is the most advantageous amount.

The reaction has been performed in ethers such as tetrahydrofuran and diethyl ether, at moderate temperatures. However, other organic solvents which are inert to the reaction conditions may be used, including halogenated alkanes such as chloroform, dichloromethane, or trichloroethane, and aromatic solvents including benzene, toluene and the xylenes. Temperatures in the range of from about ambient temperature to about 150 °C may be used; temperatures from about ambient temperature to about 80 °C are preferred, however. Economically-acceptable yields have been obtained in reaction times ranging from a few minutes to a few hours. One should note that the reaction is exothermic, and the mixture may need to be cooled, depending on the scale of the reaction and the rate at which the reactants are added.

The product of the first reaction is an alkyl 3-dioxolanyl-2,2-difluoro-3-hydroxypropionate of the formula

\[
\begin{align*}
R^{10} & \quad \text{O} \\
R^{11} & \quad \text{CO}_2\left(C_1-C_4\text{ alkyl}\right)
\end{align*}
\]

in which \( R^{10} \) and \( R^{11} \) are as described above.

The ratio of the 3-R-hydroxy intermediate to its 3-S-hydroxy enantiomer is usually about 3:1. The 3-R-hydroxy enantiomer has the proper stereochemistry to produce the ribose derivative in its natural
configuration, add so it is the desired enantiomeric product of the first step. The 3-R-hydroxy enantiomer can generally be separated cleanly from the 3-S-enantiomer by chromatography on silica gel, eluting with chloroform containing 0.5% methanol.

The hydroxypropionate, in either form, is hydrolyzed using very mild conditions to form the lactone of the formula

![Diagram]

Proper control of the hydrolysis step will cleave the ketoide function and the ester group, providing the lactone in a single step. The hydrolysis reagent preferably is a mildly acidic ion exchange resin, of which Dowex 50WX-12 (Dow Chemical Company) is most highly preferred. Other mild hydrolytic reagents may be employed although larger amounts of by-products may be obtained. For example, aqueous acetic acid, or other relatively strong acids such as propionic acid, formic acid, chloroacetic acid, or oxalic acid may be used for the hydrolysis.

The hydroxy groups of the lactone should be protected before its keto oxygen is reduced. The usual reaction conditions are used, depending on the protecting groups chosen. For example, the t-butyldimethyl-silyl group is most conveniently provided in the form of its trifluoromethanesulfonate, and the protection reaction is carried out in the presence of a base such as lutidine pyridine and the like. Acyl protecting groups such as acetyl, benzoyl and the like are added by reacting the lactone with an acylating agent such as an acyl chloride, bromide, cyanide or azide, or with an appropriate anhydride. The reactions are conveniently carried out in a basic solvent such as pyridine, quinoline or isoquinoline, or in a tertiary amine solvent such as triethylamine, tributylamine, or methylpipiridine. The reaction also may be carried out in an inert solvent, to which an acid scavenger, such as a tertiary amine, has been added. Acylation catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine may be used in the reaction, if desired. The acylation reactions which provide protecting groups on the hydroxy groups are carried out at moderate temperatures in the range of -25°C to 100°C. Such acylations also may be performed by acid-catalyzed reactions of the appropriate carboxylic acids, in inert organic solvents or neat. Acid catalysts such as sulfuric acid, polyphosphoric acid, or methanesulfonic acid may be used.

Acyl protecting groups may also be provided by forming an active ester of the appropriate acid, for example esters formed by reaction with reagents such as dicyclohexylcarbodiimide, acylimidazoles, nitrophenols, pentachlorophenol, N-hydroxysuccinimide and 1-hydroxybenzotriazole.

Protected groups of the ether type are produced by reacting the lactone with, for example, an appropriate diazo compound, such as diazomethane, phenylazomethane or a silyldiazomethane. Such reactions commonly are carried out in solvents including esters such as ethyl acetate, halogenated solvents including dichloromethane and chloroform, and ethers including diethyl ether and tetrahydrofuran. The process is usually carried out at low temperatures from about -50°C to about 0°C. Such ether-forming reactions may also be carried out with the assistance of reagents such as trimethyloxosulfonium hydroxide, trimethylsulfonium hydroxide and trimethylselenonium hydroxide, in solvents such as dimethylsulfoxide, dimethylformamide, hexamethylphosphoramide, acetone, or acetonitrile.

The silyl protecting groups discussed above are placed on the hydroxy groups by the conventional methods, such as by reaction with the appropriate silylcarboxamide or bis(substituted-silyl)carboxamide, or an appropriately substituted silazane. Suitably substituted silyl methanesulfonates, toluenesulfonates and the like are useful also. An equivalent amount of a base is usually necessary in the reaction mixture, unless a basic solvent is used in the reaction.

When the hydroxy groups have been protected, the keto oxygen of the lactone is reduced to the alcohol, forming the protected 2-desoxy-2,2-difluoro ribose or xylose. The most preferred reducing agent is disobutyl aluminum hydride, used at a low temperature in the range of about -100°C to -20°C. The reduction must be performed very carefully to avoid conditions so vigorous that the ring is opened at the oxygen atom. Other metal hydrides, such as the widely used lithium aluminum hydride, can also be used for the reduction, but it is necessary to keep the temperature quite low and to assure that the hydride is destroyed before the temperature is allowed to rise above about -20°C. Accordingly, a solvent with a very low freezing point, such as toluene, must be used in the reduction step. Other solvents, of course, can be
used, including lower alkanols, especially ethanol, or ethers such as diethyl ether.

To obtain efficient reaction with the base, an appropriate leaving group must be placed at the 1-position of the carbohydrate. The preferred leaving group is methanesulfonyl, and the compound with this leaving group is readily provided by reaction with methanesulfonyl chloride in the presence of an equivalent amount of a suitable acid scavenger such as triethylamine and the like. Other sulfonyl leaving groups are provided in the same way by reaction with the appropriate sulfonyl halide.

When a chloro or bromo leaving group is to be used, it is frequently advantageous first to make the 1-acetate derivative, as by reaction with acetic anhydride, or another source of acetyl groups, in the presence of an equivalent amount or more of an acid scavenger. The acetate group then is displaced, at a low temperature such as about -50°C to about 0°C, with gaseous hydrogen bromide or hydrogen chloride. Because the gaseous hydrogen halide may tend to remove the protecting groups, especially silyl protecting groups, operating this step at low temperatures and adding the hydrogen halide slowly in small increments is necessary.

The compounds employed in the present invention having a base portion which is composed of a purine substrate are preferably synthesized by reacting the 1-hydroxy analog of the carbohydrate having protecting groups at the 3- and 5-position with the base in the presence of diethyl azodicarboxylate and triphenylphosphine. Standard modifications are then made to the purine substrate if desired.

The bases used to form the compounds employed in the present invention are known to those skilled in the art, and no discussion of their synthesis is necessary. The primary amino groups present on some of the bases, however, should be protected before the base is coupled with the carbohydrate. The usual amino-protecting groups are employed, including silyl groups such as those have been discussed, as well as such typical groups as t-butoxy carbonyl, benzyl oxy carbonyl, 4-methoxy benzyl oxy carbonyl, 4-nitro benzyl oxy carbonyl, formy, or acetyl.

Converting the keto oxygen atoms on the bases to the enol form, in order to make the base more highly aromatic and allowing a more ready attack of the base by the carbohydrate is advisable. Enolization is provided most conveniently by producing the silyl protecting groups. The usual silyl protecting groups, as discussed above, may be used for this purpose.

The reaction between the protected carbohydrate and the base preferably is performed neat at a temperature in the range of from about 50°C to about 200°C. Use of relatively high-boiling solvents for the reaction, such as dimethylformamide, dimethylacetamide, or hexamethylyphosphoramide, however, is possible. If the coupling reaction is carried out at elevated pressures to avoid distillation of a low-boiling solvent, any convenient inert reaction solvent can be used.

The coupling reaction may be done at low temperatures if a reaction initiator, such as trifluoromethanesulfonyl oxy silane, is used. The usual inert reaction solvents, as discussed above, may be used at temperatures in the range of from about ambient temperature to about 100°C.

The final step of the reaction sequence is the removal of the protecting groups. Most silyl protecting groups are cleaved easily by contact with water or an alcohol. The t-butyldimethylsilyl protecting group requires acid conditions, such as contact with gaseous hydrogen halide, for its removal.

Acyl protecting groups are removed by simple hydrolysis with strong or moderately strong bases, such as alkali metal hydroxides, at temperatures from about ambient temperature to about 100°C. At least one equivalent amount of base is needed for each protecting group. Such hydrolyses conveniently are carried out in hydroxylic solvents, especially aqueous alkanols. The reactions also may be carried out, however, in any convenient solvent, such as polyols including ethylene glycol, ethers such as tetrahydrofuran, ketones such as acetone and methyl ethyl ketone and other polar solvents such as dimethysulfoxide. The cleavage of acyl protecting groups may also be performed with other bases, including, for example, sodium methoxide, potassium t-butoxide, hydrazine, hydroxylamine, ammonia, alkali metal amides and secondary amines such as diethylamine. The acyl protecting groups also can be removed with acid catalysts, such as methanesulfonic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, or with acidic ion exchange resins. Carrying out such hydrolyses at a relatively high temperature, such as the reflux temperature of the mixture is preferred, but temperatures as low as ambient may be used when particularly strong acids are used.

The removal of protecting groups which are ethers is carried out by known methods, for example, with ethanethiol and aluminum chloride.

Compounds of the invention possessing hydroxy or amino acyl or alkyl groups can, of course, be either selectively deprotected, or such groups may be removed and selectively replaced by standard conditions.

None of the reaction steps require unusual excesses of the reactants. As usual in organic syntheses, use of a moderate excess, in the range of 1.05X to 2X, is advisable.

The compounds employed in this invention are capable of forming pharmaceutically-acceptable addition salts. Such salts are to be construed as included within the scope of this invention and may include
hydrobromide, hydrochloride, mono-, di- or triphosphate esters and sodium salts of such phosphates, sulfate, the sodium, potassium, lithium or ammonium salts, as well as others well-known to those skilled in the art. "Pharmaceutically-acceptable salts" are those salts useful in the chemotherapy of warm-blooded animals.

One skilled in the art would be aware of the bases which are used in the synthesis of the nucleosides employed in the present invention, but the following specific nucleosides are given to further elaborate the type of agents which may be used in this invention.

1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-chloro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-bromo-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-iodo-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluororibose
1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-fluoro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-chloro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-fluoro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluororibose
1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose

or the pharmaceutically-acceptable salts thereof.

The following non-limiting Examples are provided to further illustrate the invention.

**Example 1**

1-(4-Amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

To 47.3 g (0.1 mol) of 3,5-bis(1-butyl(dimethyl)silyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose in 940 ml of dry 1,2-dichloroethane was added 48.0 g (0.16 mol) of bis-trimethylsilyl N-acetylcytosine followed by 39.23 g (0.177 mol) of trifluoromethanesulfonyloxytrimethylsilane. The reaction mixture was refluxed under a nitrogen atmosphere for about 15 hours, cooled to room temperature, and diluted by the addition of 16 ml of methanol. The resulting mixture was stirred for 30 minutes, concentrated under vacuum to about one-half the original volume and cooled in ice. The precipitated solid was collected by filtration and the filtrate was shaken one time with about 300 ml of 10% sodium bicarbonate and one time with brine. The organic layer was separated and concentrated to dryness in vacuo at 45 °C. The residue was dissolved into 1.3 I. of methanol saturated with ammonia and the resulting solution was stirred overnight. The volatiles were removed in vacuo at 45 °C to provide 32 g of residue. The residue was dissolved into 275 ml of methanol and 100 g of Biorad cation exchange resin (AG50WX8) was added to the resulting solution. The suspension was stirred at ambient temperature overnight. The resin was removed by filtration and rinsed one time with 100 ml of methanol. The filtrate was discarded and the resin was suspended in 100 ml of methanol and 50 ml of concentrated ammonium hydroxide. This mixture was stirred vigorously for 15 minutes and the resin was filtered. This procedure was repeated twice with additional fresh methanolic ammonia. The basic methanolic filtrates were combined and evaporated at 45 °C in vacuo to yield a brown foam weighing 13.8 grams. This material was chromatographed with the use of a Waters Prep 500 C18 reverse phase column with 100% water to yield 1.26 g of 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose.

NMR (CD3OD, 90 MHz, δ) 3.7-4.65 (m, 4H), 4.83 (s, 4H), 5.97 (d, J = 8Hz, 1H), 6.24 (t, J = 7Hz, 1H), 7.88 (d, J = 8Hz, 1H).

Mass spec. m/z = 263 = P

**Example 2**

1-(4-Amino-5-iodo-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

To 1.99 g (0.0042 mol) of 3,5-bis(1-butyl(dimethyl)silyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose in 35 ml of dry 1,2-dichloroethane was added 2.08 g (0.0046 mol) of tris-trimethylsilyl-5-
iodocytosine followed by 1.11 g (0.005 mol) of trifluoromethanesulfonyloxytrimethylsilane. The reaction mixture was refluxed for about 16 hours under a nitrogen atmosphere and cooled to room temperature. Five milliliters of methanol were added to the reaction mixture and the mixture was stirred for an additional 30 minutes. The mixture was filtered and the precipitated solid was collected by filtration. The filtrate was evaporated to dryness under reduced pressure, and the resulting residue was dissolved in 20 ml of dichloromethane saturated with anhydrous hydrogen bromide. This mixture was stirred for about 3 hours. The volatiles were removed in vacuo at 45 °C. The residue was dissolved in 15 ml of water, neutralized with 10% sodium bicarbonate, and the resulting solution was washed once with 10 ml of ethyl acetate. The aqueous layer was chromatographed on a Whatman Prep ODS-3 reverse phase column in 2.0 ml portions using water/methanol (9:1, v:v) to afford 30 mg of 1-(4-amino-5-ido-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose.

NMR (CD₃OD, 90 mHz, δ) 3.47-4.66 (m, 4H), 4.78 (s, 4H), 6.14 (t, J = 7Hz, 1H), 8.32 (s, 1H).
Mass spec. m/e = 389 = P

Example 3

1-(2,4-Dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

A solution of 190 mg (0.0007 mol) of 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoro ribose in 16 ml of glacial acetic acid and 4 ml of water was refluxed for approximately 24 hours. The reaction mixture was cooled to ambient temperature and the volatiles were evaporated under vacuum at about 60-70 °C. The residue was stirred with 5.0 ml of toluene and the resulting solution was evaporated several times. The residue was dissolved in 12 ml of methanol, and the resulting mixture was cooled to -15 °C and saturated with anhydrous ammonia. The solution was stirred overnight at ambient temperature. The volatiles were removed in vacuo at 45 °C. The residue was suspended in about 5.0 ml of hot water and the insoluble material was removed by filtration. The filtrate was chromatographed on a Whatman 50 cm partil ODS-3 reverse phase column using water/methanol (9:1, v:v) as the eluent to afford 0.05 g of product containing a small trace of unreacted starting material. The unreacted starting material was removed by passing a solution of 0.05 g of the mixture in about 5.0 ml of a solvent solution of methylene chloride/methanol (9:1, v:v) through a Waters Silica Sep-Pak. The eluate was evaporated in vacuo at 45 °C to yield 0.036 g of 1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose.

NMR (CD₃OD, 90 mHz, δ) 3.54-4.48 (m, 4H), 4.83 (s, 3H), 5.69 (d, J = 8Hz, 1H), 6.10 (dd, J = 7Hz, 9Hz, 1H), 7.8 (d, J = 8Hz, 1H).
Mass spec. m/e = 264 = P

Example 4

1-(4-Amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

A solution of 1.86 g (0.0039 mol) of 3,5-bis(t-butydimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose, 1.87 g (0.0055 mol) of bis-trimethylsilyl-5-methylcytosine and 1.34 g (0.006 mol) of trifluoromethanesulfonyloxytrimethylsilane in 37 ml of dry methylene chloride was refluxed overnight. The reaction mixture was cooled to room temperature and 1.0 ml of methanol was added thereto. The precipitated solid was collected by filtration and the filtrate was evaporated in vacuo at 45 °C. The residue was dissolved in 20 ml of water and the resulting solution was concentrated to about 10 ml in vacuo at 50 °C at which point a precipitate formed. The precipitated solid was collected by filtration and the filtrate was concentrated in vacuo at 50 °C to afford 2.2 g of residue. The residue was triturated several times with 10 ml portions of warm acetone. The decanted organic layers were combined and evaporated in vacuo at 45 °C to provide 1.87 g of a yellow oil. This material was dissolved into 15 ml of methanol/water (v:v, 1:1) and the resulting solution was stirred overnight with 5.0 g of Biorad AG50W-X8. The suspension was saturated with anhydrous ammonia and stirred for 10 minutes. The resin was collected by filtration and suspended in 30 ml of methanol/ammonia (v:v, 2:1). The solution was stirred for 10 minutes. The resin was collected by vacuum filtration, and the basic filtrates were combined and concentrated in vacuo at 50 °C to provide 1.5 g of an orange oil. The oil was dissolved in 10 ml of water and chromatographed 2.0 ml per run on a Whatman partisil ODS-3 50 cm reverse phase prep column using water as the eluent to provide 0.07 g of 1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose.

NMR (CD₃OD, 90 mHz, δ) 1.94 (s, 3H), 3.53-4.62 (m, 4H), 4.75 (s, 4H), 6.17 (t, J = 8Hz, 1H), 7.67 (s, 1H).
Example 5

1-(4-Amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

Under a nitrogen atmosphere, to 17.89 g (0.0375 mol) of 3,5-bis(t-butyldimethylsiloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose in 300 ml of dry methylene chloride was added 23.0 g (0.063 mol) of tris-trimethylsilylacetamide followed by 10.84 g (0.0488 mol) of trifluoromethanesulfonyl-
trimethylsilane. The solution was refluxed overnight and cooled to room temperature. Twenty milliliters of methanol were added to the reaction mixture and the resulting solution was stirred vigorously for about one hour. The precipitated solid was collected by filtration. The filtrate was charged with 100 ml of water and the suspension was stirred vigorously for 30 minutes. The organic layer was separated and concentrated in vacuo at 45 °C to give 11.2 g of a brown oil. The oil was dissolved in 95 ml of methanol to which 33 g of Biorad AG50Wx8 cation exchange resin had been added and the suspension was stirred overnight at ambient temperature. The resin was collected by filtration and washed with 50 ml of methanol. The resin was stirred vigorously with 100 ml of a solution of methanol/ammonia (v/v, 1:1). The resin was collected by filtration and again stirred in this solution. The resin was collected and the basic filtrates were combined and concentrated in vacuo at 50 °C to give 2.09 g of a yellow residue. This material was suspended in 25 ml of water and stirred vigorously for 15 minutes. The insoluble precipitate was filtered to yield 0.250 g of a compound labeled A. The filtrate was concentrated in vacuo at 50 °C to yield 0.86 g of a compound labeled B. Compound A was dissolved in 20 ml of methanol and stirred for 3 days with Biorad AG50Wx8 at ambient temperature. The resin was collected by filtration and slurried in 30 ml of a solution of methanol/concentrated ammonium hydroxide (v/v, 1:1). The resin was collected by filtration and the filtrate concentrated in vacuo at 50 °C to give 0.14 g of 1-(2-desoxy-2,2-difluoro-α-D-xylufuranosyl)cytosine.

NMR (CD$_3$OD, 90 MHz, δ) 3.72-4.34 (m, 4H), 4.78 (s, 4H), 5.86 (d, J = 8Hz, 1H), 6.17 (d, J = 15Hz, 1H), 7.78 (d, J = 8Hz, 1H).
Mass spec. m/e = 263 = P

The compound labeled B was chromatographed on a Whatman 50 cm ODS-3 reverse phase prep column using water/methanol (v/v, 1:1) as the eluent to afford 0.06 g of 1-(2-desoxy-2,2-difluoro-α-D-xylufuranosyl)cytosine.

NMR (CD$_3$OD, 90 MHz, δ) 3.53-3.9 (m, 2H), 4.1-4.57 (m, 2H) 4.83 (s, 4H), 5.9 (d, J = 8Hz, 1H), 6.3 (dd, J = 7Hz, 12Hz, 1H) 7.55 (d, J = 8Hz, 1H).
Mass spec. m/e = 263 = P

Example 6

1-(6-Amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose

A. 1-(6-Chloro-9H-purin-9-yl)-3,5-bis(t-butyldimethylsiloxy)-2-desoxy-2,2-difluororibose

To a solution of 0.77 g (5.0 mmol) of 6-chloropurine in 50 ml of tetrahydrofuran was added 1.31 g (5.0 mmol) of triphenylphosphine and 0.87 g (5.0 mmol) of diethyl azodicarboxylate. To this solution was added a solution of 1.99 g (5.0 mmol) of 3,5-bis(t-butyldimethylsiloxy)-1-hydroxy-2-desoxy-2,2-difluororibose in tetrahydrofuran. The reaction mixture was stirred at room temperature for approximately 60 hours and an additional 0.66 g (1.7 mmol) of 3,5-bis(t-butyldimethylsiloxy)-1-hydroxy-2-desoxy-2,2-difluororibose was added to the reaction mixture. The mixture was stirred for an additional 6 hours at room temperature. The solvent was evaporated under vacuum and the residue was stirred in a small amount of diethyl ether overnight. The precipitated solid was removed by vacuum filtration and the filtrate was concentrated under vacuum to dryness. The residue was chromatographed over 70 g of silica and eluted with chloroform. Fractions containing the major component were combined and the solvent was evaporated therefrom to provide 1.0 g of 1-(6-chloro-9H-purin-9-yl)-3,5-bis(t-butyldimethylsiloxy)-2-desoxy-2,2-difluororibose. The structure of the product was verified by NMR. Mass spec. = 477 [534-(t-butyli)]

B. 1-(6-Amino-9H-purin-9-yl)-3,5-bis(t-butyldimethylsiloxy)-2-desoxy-2,2-difluororibose

A solution of 0.5 g (0.936 mmol) of 1-(6-chloro-9H-purin-9-yl)-3,5-bis(t-butyldimethylsiloxy)-2-desoxy-2,2-difluororibose dissolved in 75 ml of absolute ethanol was saturated with anhydrous ammonia at about 0 °C. The reaction flask was sealed, and the mixture was allowed to warm to room temperature. The mixture was stirred for about 72 hours at room temperature and the volatiles were evaporated under
reduced pressure to provide 420 mg of 1-(6-amino-9H-purin-9-yl)-3,5-bis[butyl(dimethyl)siloxyl]-2-desoxy-2,2-difluorouribose.

Mass spec = 458 [M+1-(butyl)]

C. A solution of 100 mg (0.194 mmol) of 1-(6-amino-9H-purin-9-yl)-3,5-bis[butyl(dimethyl)siloxyl]-2-desoxy-2,2-difluorouribose dissolved in 25 ml of methylene chloride cooled to about 0 °C with an external ice bath was saturated with anhydrous hydrogen bromide gas. The mixture was stirred at about 0 °C for about 4 hours, and nitrogen was bubbled through the reaction mixture. The mixture was filtered and the collected solid was washed with methanol to provide 110 mg of solid. The solid was purified by HPLC to provide 12.1 mg of β-1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluorouribose.

NMR (CD3OD, 30 MHz, δ): 3.8-4.65 (m, 4H); 4.83 (bs, 4H); 6.33 (dd, 1H); 8.22 (s, 1H); 8.4 (s, 1H). mass spec. m/e = 287

Example 7

A. 1-(2,6-Dichloro-9H-purin-9-yl)-3,5-bis[butyl(dimethyl)siloxyl]-2-desoxy-2,2-difluorouribose

To a solution of 1.89 g (10.0 mmol) of 2,6-dichloropurine in 100 ml of tetrahydrofuran was added 2.62 g (10.0 mmol) of triphenylphosphine and 1.74 g (10.0 mmol) of diethyl azodicarboxylate. To this mixture was added a solution of 3.96 g (10.0 mmol) of 3,5-bis[butyl(dimethyl)siloxyl]-1-hydroxy-2-desoxy-2,2-difluorouribose in 25 ml of tetrahydrofuran and the mixture was stirred at room temperature overnight.

The precipitated solid was removed by vacuum filtration and the filtrate was concentrated under vacuum.

The residue was dissolved in 100 ml of diethyl ether and the solution was stirred at room temperature overnight. The mixture was filtered and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in 25 ml of ethyl acetate, and the mixture was set in the refrigerator. The mixture was filtered and the filtrate was chromatographed by HPLC while eluting with hexane/ethyl acetate (4/1, v/v). The first chromophore containing fractions were combined and the solvent was evaporated therefrom to provide 2.5 g of 1-(2,6-dichloro-9H-purin-9-yl)-3,5-bis[butyl(dimethyl)siloxyl]-2-desoxy-2,2-difluorouribose. m/e = [568-(butyl)] = 511

B. 1-(2-Chloro-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose and 1-(2-chloro-6-bromo-9H-purin-9-yl)-2-desoxy-2,2-difluorouribose

A solution of 0.5 g (0.88 mmol) of 1-(2,6-dichloro-9H-purin-9-yl)-3,5-bis[butyl(dimethyl)siloxyl]-2-desoxy-2,2-difluorouribose dissolved in 100 ml of methylene chloride cooled to about 0 °C was saturated with anhydrous hydrogen bromide gas. The mixture was stirred at 0 °C for about 7 hours and then at room temperature for about 16 hours. The mixture was filtered, and the precipitated solid was dissolved in methanol. The methanolic solution was concentration under vacuum to provide 160 mg of a mixture of 1-(2-chloro-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose and 1-(2-chloro-6-bromo-9H-purin-9-yl)-2-desoxy-2,2-difluorouribose as a light yellow solid. m/e = 322 and 386 respectively.

C. 1-(2-Chloro-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose

A mixture of 1.18 g (3 mmol) of 1-(2-chloro-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose and 1-(2-chloro-6-bromo-9H-purin-9-yl)-2-desoxy-2,2-difluorouribose dissolved in 11 ml of 1.0 N sodium hydroxide was stirred at room temperature for three hours. The pH of the mixture was lowered to about 7 with 2N hydrochloric acid. The mixture was concentrated under vacuum at about 45 °C. The residue was slurried in warm methanol, filtered and this procedure was repeated. The filtrates were combined and the solution was concentration under vacuum at 15 °C to provide 1.36 g of 1-(2-chloro-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose. m/e = 322.

D. This is the preferred synthesis of 1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose. The material prepared by the following reaction was used as a reference standard for the subsequent synthesis of the compound which was biologically evaluated.

To a suspension of 1.3 g of 1-(2-chloro-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose in 30 ml of absolute ethanol at a temperature of about 0 °C was added anhydrous ammonia. The mixture was placed in a closed reaction vessel and heated at about 150 °C overnight. The mixture was cooled and the solid was collected. The filtrate was suspended in 15 ml of hot methanol and the mixture was again filtered. The filtrate was concentration under vacuum and the residue was chromatographed by HPLC using water/methanol (9/1, v/v) as the eluent at a flow rate of 4 ml/minute to provide 10 mg of α-1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose and 5 mg of β-1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose. m/e = 303

The compounds which were biologically tested were prepared as follows:

To 0.28 g of a mixture of 1-(2-chloro-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorouribose and 1-(2-chloro-6-bromo-9H-purin-9-yl)-2-desoxy-2,2-difluorouribose in 10 ml of absolute ethanol at about 0 °C was
added anhydrous ammonia for 20 minutes. The flask was sealed and placed in an oil bath at about 150 °C
for about 16 hours. The volatiles were evaporated under reduced pressure and the residue was purified by
standard procedures to provide 9.6 mg of α-1-(2-chloro6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose
having m/e = 322; 8.2 mg of β-1-(2-chloro6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose having m/e
= 322 and an NMR (CD3OD, 300 mHz, δ) 3.8-4.85 (m, 4H); 4.93 (bs, 4H); 6.25 (dd, 1H); 8.35 (s, 1H); 6.5
mg of a mixture of α- and β-1-(2,6-diamino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose having (m + l)/e =
304 and m/e calc. 303.1017; obs. 303.1009; 9.0 mg of 1-(2-amino-6-oxide-1H,9H-purin-9-yl)-2-desoxy-2,2-
difluororibose having (m + H)/e and calc. 304.0857; obs. 304.0857; and NMR (CD3OD, 300 mHz, δ) 3.85-4.85
(m, 4H); 4.9 (bs, 5H); 6.15 (dd, 1H); 7.98 (s, 1H); and 9.0 mg of α- and β-1-(2,6-dioxo-1H,3H,9H-purin-9-yl)-
2-desoxy-2,2-difluororibose having m/e = 304.

The present invention provides a method of treating susceptible neoplasms in mammals comprising
administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound
of formula I. The method comprises administering the compound to the mammal by various routes
including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes.

The term ”pharmaceutically effective amount” refers to an appropriate amount of a compound of
formula I which is capable of providing chemotherapy to mammals. The active compounds are effective
over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.1 to
about 1200 mg/kg of body weight. In the treatment of adult humans, the range of about 0.1 to about 50
mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of compound
actually administered will be determined by a physician, in the light of the relevant circumstances including
the condition to be treated, the particular compound to be administered, the chosen route of administration,
the age, weight, and response of the individual patient, and the severity of the patient’s symptoms, and
therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

The term ”susceptible neoplasm”, as defined herein, represents an abnormal growth of tissue in
mammals capable of being treated by a compound of formula I. While the compounds of formula I are
effective against tumors, both solid and non-solid type, the compounds are effective in controlling the
growth of rapidly dividing cells because of the compounds’ cytotoxic nature. It is a special feature of these
compounds that they have a broad spectrum of activity, and are accordingly useful against a variety of
tumors.

The compounds of the present method are preferably administered as a pharmaceutical formulation.
Therefore, as yet another embodiment of the present invention, a pharmaceutical formulation useful for
treating susceptible neoplasms in mammals is provided comprising a compound of formulæ II or III in
combination with a pharmaceutical carrier, diluent or excipient therefor.

The active ingredient will be present in the formulation in the range of about 1% to about 90% by
weight. The active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within
a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves
as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for
the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges,
sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid
medium), ointments containing for example up to 10% by weight of the active compound, soft and hard
gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol,
mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, micro-
crystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methyl cellulose, methyl- and propyl-
hydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include
lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening
agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick,
sustained release of the active ingredient after administration to the patient by employing procedures well
known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5
to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term “unit dosage
form” refers to physically discrete units suitable as unitary dosages for human subjects and other
mammals, each unit containing a predetermined quantity of active material calculated to produce the
desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The following formulation examples represent specific pharmaceutical formulations employing com-
ounds comprehended by the present method. The formulations may employ as active compounds any of
the compounds of Formula I. The examples are illustrative only and are not intended to limit the scope of
the invention in any way.
EP 0 184 365 B1

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

<table>
<thead>
<tr>
<th></th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>250</td>
</tr>
<tr>
<td>Starch dried</td>
<td>200</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>10</td>
</tr>
</tbody>
</table>

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

A tablet formula is prepared using the ingredients below:

<table>
<thead>
<tr>
<th></th>
<th>Quantity (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>250</td>
</tr>
<tr>
<td>Cellulose, microcrystalline</td>
<td>400</td>
</tr>
<tr>
<td>Silicon dioxide, fumed</td>
<td>10</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>5</td>
</tr>
</tbody>
</table>

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

<table>
<thead>
<tr>
<th></th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.25</td>
</tr>
<tr>
<td>Ethanol</td>
<td>29.75</td>
</tr>
<tr>
<td>Propellant 22 (Chlorodifluoromethane)</td>
<td>70.00</td>
</tr>
</tbody>
</table>

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then placed in a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets each containing 60 mg of active ingredient are made up as follows:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>60 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>45 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>35 mg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (as 10% solution in water)</td>
<td>4 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl starch</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

The difluororibonucleoside starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50 °C - 60 °C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are
compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules each containing 80 mg of medicament are made as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxyllose</td>
<td>80 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>59 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>59 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories each containing 225 mg of nucleoside are made as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>225 mg</td>
</tr>
<tr>
<td>Saturated fatty acid glycerides to</td>
<td>2 g</td>
</tr>
</tbody>
</table>

The nucleoside is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>50 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose</td>
<td>50 mg</td>
</tr>
<tr>
<td>Syrup</td>
<td>1.25 ml</td>
</tr>
<tr>
<td>Benzoic acid solution</td>
<td>0.10 ml</td>
</tr>
<tr>
<td>Flavor</td>
<td>q.v.</td>
</tr>
<tr>
<td>Color</td>
<td>q.v.</td>
</tr>
<tr>
<td>Purified water to</td>
<td>5 ml</td>
</tr>
</tbody>
</table>

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation is prepared as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoro ribose</td>
<td>100 mg</td>
</tr>
<tr>
<td>Isotonic saline</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>

The solution of the above ingredients is administered intravenously at a rate of 1 ml/minute to a mammal in need of treatment from susceptible neoplasms.

The activity of representative compounds employed in the present invention has been demonstrated in standard screens commonly used by those in the art for testing compounds with potential antitumor activity. For example, these screens have been used to demonstrate the antitumor activity of commercially available
cancer drugs such as the vinca alkaloids. See, e.g., Miller et al., in J. Med. Chem. Vol. 20, No. 3 409 (1977) and Sweeney, et al., in Cancer Research 38, 2886 (1978).

The compounds represented by formula I are cytostatic in that they inhibit the growth of human leukemic cells (CCRF-CEM cell line). Table 1 below gives the results of the testing of several compounds representative of those of Formula I. In the Table, column 1 gives the name of the compound and column 2 the IC₅₀ (concentration giving 50% growth inhibition) in mcg/ml.

Table 1

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>IC₅₀ mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.0039</td>
</tr>
<tr>
<td>0.0057</td>
<td></td>
</tr>
<tr>
<td>0.0068</td>
<td></td>
</tr>
<tr>
<td>0.0206</td>
<td></td>
</tr>
<tr>
<td>1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoropylase</td>
<td>0.3</td>
</tr>
<tr>
<td>1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>5.4</td>
</tr>
<tr>
<td>1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.3</td>
</tr>
<tr>
<td>β-1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.5</td>
</tr>
<tr>
<td>α-1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose</td>
<td>6.9</td>
</tr>
<tr>
<td>α-1-(2-chloro-6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose</td>
<td>&gt;20.0</td>
</tr>
<tr>
<td>β-1-(2-chloro-6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.4</td>
</tr>
<tr>
<td>1-(2,6-diamino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.075</td>
</tr>
<tr>
<td>1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.10</td>
</tr>
<tr>
<td>1-(2,6-dioxo-1H,3H,9H-purin-9-yl)-2-desoxy-2,2-difluororibose</td>
<td>0.30</td>
</tr>
</tbody>
</table>

To further demonstrate the ability of the compounds of formula I to treat susceptible neoplasms in mammals, the compounds of Example 1, 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose, Example 5, 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoropylase, and Example 6, 1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose, were tested in animals bearing a tumor system representative of L1210V lymphocytic leukemia.

The study testing the efficacy of these compounds against L1210V leukemia was initiated by an IP inoculation of 1 X 10⁶ cells. Treatment was begun 24 hours after inoculation. The response to therapy was determined by comparing the mean life span of the ten treated animals to that of the ten control animals; prolongation of life in the treated animals beyond that of controls is expressed as a percentage. Table 2 gives the results of several experiments in mice bearing this tumor. In the Table, column 1 gives the example number of the compound tested; column 2, the experiment number; column 3, the dose level of the compound in mg/kg; column 4, the route of administration; column 5, the dosage schedule, that is, the days on which the compound was administered to the mice; column 6, the average increase in life span of the treated mice as compared to the control mice; column 7, the toxic deaths over the number of mice in each group; and column 8, the indefinite survivors, that is, the number of 45 day survivors in each group.
### Table 2

**L1210V Lymphocytic Leukemia Tumor System**

<table>
<thead>
<tr>
<th>Example No. of Compound Tested</th>
<th>Experiment No.</th>
<th>Dose Level mg/kg</th>
<th>Route of Administration</th>
<th>Dosage Schedule</th>
<th>Percent Increase Life Span</th>
<th>Toxic Deaths</th>
<th>Indefinite Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20.0</td>
<td>IP</td>
<td>Days</td>
<td>60</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.0</td>
<td></td>
<td>1,5,9</td>
<td>66</td>
<td>1/10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0</td>
<td></td>
<td></td>
<td>66</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td></td>
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<td>2.5</td>
<td></td>
<td></td>
<td>60</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.25</td>
<td></td>
<td></td>
<td>50</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>200.0</td>
<td>IP</td>
<td></td>
<td>Day 1 only</td>
<td>34</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>IP</td>
<td></td>
<td></td>
<td>26</td>
<td>0/10</td>
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<tr>
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<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
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<td></td>
<td>23</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
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<td>Daily</td>
<td></td>
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<td>4/10</td>
<td>0</td>
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<tr>
<td></td>
<td>2.0</td>
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<td>for 10 days</td>
<td></td>
<td>18</td>
<td>1/10</td>
<td>0</td>
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<tr>
<td></td>
<td>1.0</td>
<td>PO</td>
<td>for 10 days</td>
<td></td>
<td>15</td>
<td>0/10</td>
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<tr>
<td></td>
<td>0.5</td>
<td>PO</td>
<td>for 10 days</td>
<td></td>
<td>8</td>
<td>0/10</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 2 (continued)

<table>
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<tr>
<th>Example No.</th>
<th>Compound Tested</th>
<th>Dose Level mg/kg</th>
<th>Route of Administration</th>
<th>Dosage Schedule</th>
<th>Percent Increase Life Span</th>
<th>Toxic Deaths</th>
<th>Indefinite Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1</td>
<td>4.0</td>
<td>IP</td>
<td>Daily</td>
<td>44</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0</td>
<td></td>
<td>for 9 days</td>
<td>136</td>
<td>0/10</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
<td>days</td>
<td>104</td>
<td>0/10</td>
<td>0</td>
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<td></td>
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<td>74</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>for 10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>200.0</td>
<td>IP</td>
<td>Daily</td>
<td>18</td>
<td>0/7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.0</td>
<td></td>
<td>for 9 days</td>
<td>16</td>
<td>0/7</td>
<td>0</td>
</tr>
</tbody>
</table>
CA755 - The adenocarcinoma 755 is an undifferentiated mammary carcinoma which was obtained in 1980 from the Division of Cancer Treatment, N.C.I., tumor bank maintained at E. G. and G. Mason Research (Worcester, MA). First passage tumor was stored in liquid nitrogen using standard techniques. The transplanted tumor was re-established from the tumor bank every six months or as needed. The tumor is maintained by serial passage once a week in C57BL/6 female mice (Jackson Laboratory; Bar Harbor, ME).

P1534J - The P1534J lymphocytic leukemia (solid form) was obtained in 1973 from the Jackson Laboratory (Bar Harbor, ME). First passage tumor was stored in liquid nitrogen using standard techniques. Subsequent replenishment of the tumor bank with this tumor was accomplished from first passage tumor. The transplanted tumor was re-established from the tumor bank every six months or as needed. The tumor is maintained by serial passage once a week in DBA/2 mice (Charles River; Wilmington, MA).

XS563 Myeloma - the tumor is maintained in C3H mice.

The following procedure was employed in demonstrating the activity of these compounds against the tumor systems. The tumor was removed from passage animals and minced into 1 to 3 mm square fragments using sterile techniques. Tumor pieces were checked for sterility using both Antibiotic Medium 1 and Brain Heart Infusion (Difco; Detroit, MI). Recipient mice were shaved and tumor pieces were implanted subcutaneously in the axillary region by trocar. Drug therapy on the appropriate schedule was initiated on the day after tumor implant. The compound was dissolved in saline for all experiments. All animals were weighed at the beginning and end of drug treatment. Food and water were provided ad libitum. On days 10 to 12, two dimensional measurements (width and length) of all tumors were taken using vernier calipers. Tumor weights were calculated from these measurements using the following formula:

\[
\text{Tumor Weight (mg)} = \text{Tumor Length (mm)} \times \text{Tumor Width (mm)}^{2}/2
\]

For all data, the tumor weight was rounded to the nearest tenth of a gram for analysis. No group is included in the analysis for therapeutic activity in which deaths attributable to drug toxicity exceeded 30 percent of the treated group.

In Table 3 which follows, column 1 gives the example number of the compound tested; column 2 provides the tumor system; column 3, the dose level; column 4, the route administered; column 5, the dosage schedule; column 6, the percent inhibition of the tumor; and column 7, the toxic deaths observed prior to completion of the study.
<table>
<thead>
<tr>
<th>Example No. of Compound Tested</th>
<th>Tumor System</th>
<th>Dose Level mg/kg</th>
<th>Route of Administration</th>
<th>Dosage Schedule</th>
<th>Percent Inhibition of Tumor</th>
<th>Toxic Deaths</th>
</tr>
</thead>
<tbody>
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<td>6C3HED</td>
<td>20.0</td>
<td>IP</td>
<td>Days</td>
<td>95</td>
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<td>10.0</td>
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<td>1,5,9</td>
<td>88</td>
<td>0/7</td>
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<td></td>
<td></td>
<td>49</td>
<td>0/7</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>1</td>
<td>0/7</td>
</tr>
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<td></td>
<td></td>
<td>0</td>
<td>0/7</td>
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<td>Days</td>
<td>94</td>
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<td>44</td>
<td>0/10</td>
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<td>0/10</td>
</tr>
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<td>Days</td>
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<td></td>
<td>30</td>
<td>0/10</td>
</tr>
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<td></td>
<td></td>
<td>1.25</td>
<td></td>
<td></td>
<td>8</td>
<td>0/10</td>
</tr>
<tr>
<td>Percent Inhibition of Tumor</td>
<td>Dosage Schedule</td>
<td>Dose Level mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td></td>
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</tr>
<tr>
<td>100</td>
<td>1,5,9 Days</td>
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<tr>
<td>11</td>
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<td>1.25</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Daily for 5 days</td>
<td>30.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The compounds employed in the present method are effectively administered orally, topically or parenterally. In general, dosage rates in the range of from about 5 mg/kg to about 500 mg/kg are useful. It is more preferred to administer at rates in the range of from about 10 mg/kg to about 100 mg/kg.
Claims
Claims for the following Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. The use of a compound of formula (I):

\[ \text{(I)} \]

in which:

- \( R^1 \) is hydrogen, C\(_1\)-C\(_4\) alkyl or

\[ \begin{align*}
  &O \\
\end{align*} \]

\[ \begin{align*}
  &\text{II} \\
  &-C-R^5;
\end{align*} \]

\( R^2 \) is a base defined by one of the formulae

\[ \begin{align*}
  &\text{NH}R^3 \\
\end{align*} \]

\[ \begin{align*}
  &\text{O} \\
  &\text{II} \\
  &\text{NH}_2 \\
\end{align*} \]

\[ \begin{align*}
  &\text{O} \\
  &\text{II} \\
  &\text{N} \\
\end{align*} \]

\[ \begin{align*}
  &\text{O} \\
  &\text{II} \\
  &\text{NH}_2 \\
\end{align*} \]

\[ \begin{align*}
  &\text{O} \\
  &\text{II} \\
  &\text{N} \\
\end{align*} \]

\[ \begin{align*}
  &\text{O} \\
  &\text{II} \\
  &\text{NH}_2 \\
\end{align*} \]

\[ \begin{align*}
  &\text{O} \\
  &\text{II} \\
  &\text{N} \\
\end{align*} \]

\( X \) is N or C-R\(_4\):

- \( R^3 \) is hydrogen, C\(_1\)-C\(_4\) alkyl or

\[ \begin{align*}
  &\text{O} \\
\end{align*} \]

\[ \begin{align*}
  &\text{II} \\
  &-C-R^5;
\end{align*} \]

\( R^4 \) is hydrogen, C\(_1\)-C\(_4\) alkyl, amino, bromo, fluoro, chloro or iodo;

each \( R^5 \) independently is hydrogen or C\(_1\)-C\(_4\) alkyl; or

a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament for the treatment
of susceptible neoplasms.

2. The use as claimed in Claim 1 in which the compound of formula (I) is 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose, 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difuorourylose, 1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose, 1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose, or a pharmaceutically-acceptable salt thereof.

3. A compound of formula (II):

\[
\begin{align*}
R^6\text{O}_2\text{C} & \quad \text{O} \\
R^7 & \quad \text{F} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{F} \\
\text{HO} & \quad \text{F} \\
\text{(II)}
\end{align*}
\]

in which:

- \(R^6\) is hydrogen or \(C_1-C_4\) alkyl;
- \(R^7\) is a pyrimidine, a 5-aza-pyrimidine or purine base of one of the formulae

\[
\begin{align*}
\text{NHR}^6 & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O}
\end{align*}
\]

- \(Q\) is \(N\), \(C-(C_2-C_4\) alkyl) or \(C\)-amino;
- \(X\) is \(N\) or \(C\)-\(R^7\);
- \(R^8\) is hydrogen or \(C_1-C_4\) alkyl;
- \(R^9\) is hydrogen, \(C_1-C_4\) alkyl, amino, bromo, fluoro, chloro and iodo or a pharmaceutically-acceptable salt thereof; with the proviso that \(R^6\) and \(R^9\), both may be hydrogen only when \(X\) is \(N\), and further provided the compound is not 1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorurylose or 1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluorurylose.

4. A compound of formula (II), as defined in claim 3 or a pharmaceutically-acceptable salt thereof for use in the chemotherapy of a mammal.
5. A compound of formula (II), or a pharmaceutically-acceptable salt thereof for use in the treatment of a susceptible neoplasm in a mammal.

6. A pharmaceutical formulation for use in treating susceptible neoplasms in mammals comprising a compound of Claim 3, or a pharmaceutically-acceptable salt thereof, in combination with a suitable pharmaceutically-acceptable carrier, diluent or excipient therefor.

7. A compound of formula (III):

![Chemical Structure](image)

in which:

- R⁶ is hydrogen or C₁-C₄ alkyl; and
- R⁹ is

![Chemical Structure](image)

or

a pharmaceutically-acceptable salt thereof.

8. A pharmaceutical formulation for use in treating susceptible neoplasms in mammals comprising a compound of Claim 7 in combination with a suitable pharmaceutically acceptable carrier, diluent or excipient therefor.

9. A compound of formula (III), as defined in claim 7, for use in the chemotherapy of a mammal.

10. A process for preparing a compound of formula (II) or (III), as defined in Claim 3 or 7, which comprises removing the protecting groups from a correspondingly protected nucleoside of formula (II) or (III).

11. A process for preparing a compound of formula (II) or (III), as defined in Claim 3 or 7, which comprises:
   (a) coupling a pyrimidine base of the formula R'H, or a protected derivative thereof, with a carbohydrate of formula IV, or a protected derivative thereof:

![Chemical Structure](image)

in which the R'H pyrimidine base and R⁶ are as defined in claim 3 and Leav is a leaving group, and
Claims for the following Contracting State: AT

1. A process for preparing a compound of formula (II):

in which:
- $R^6$ is hydrogen or $C_1$-$C_6$ alkyl;
- $R^7$ is a pyrimidine or purine base of one of the formulae

- Q is N, C-$(C_2$-$C_6$ alkyl) or C-amino;
- X is N or C-$R^7$;
- $R^8$ is hydrogen or $C_1$-$C_6$ alkyl;
- $R^9$ is hydrogen, $C_1$-$C_6$ alkyl, amino, bromo, fluoro, chloro and iodo; or

a pharmaceutically-acceptable salt thereof; with the proviso that $R^8$ and $R^9$, both may be hydrogen only when X is N and further providing the compound is not
2. A process for preparing a compound of formula (II):

in which:
- R⁶ is hydrogen or C₁-C₄ alkyl;
- R⁷ is a pyrimidine, a 5-aza-pyrimidine or purine base of one of the formulae

Q is N, C-(C₂-C₄ alkyl) or C-amino;
X is N or C-R⁴;
R⁴ is hydrogen or C₁-C₄ alkyl;
R⁸ is hydrogen, C₁-C₄ alkyl, amino, bromo, fluoro, chloro and iodo; or
a pharmaceutically-acceptable salt thereof; with the proviso that R⁶ and R⁷, both may be hydrogen only when X is N and further providing the compound is not
1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluoroxylose or
1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluoroxylose which comprises:
(a) coupling a pyrimidine base of the formula $R^H$, or a protected derivative thereof, with a carbohydrate of formula IV, or a protected derivative thereof:

\[
\begin{align*}
\text{IV} & \quad \text{(IV)} \\
R^6\text{OCH}_2 & \quad \text{CH-(Leav)} \\
\text{HO} & \quad \text{F} \\
\text{F} & \quad \text{F}
\end{align*}
\]

in which the $R^H$ pyrimidine base and $R^6$ are as defined above and Leav is a leaving group, and if desired, removing any protecting group present to produce the pyrimidine base product; and

(b) if a formula (III) or formula (II) compound in which the base is a purine is desired, reacting with ammonia a corresponding purine nucleoside compound in which a C-2 and/or C-6 substituent of the purine portion of the compound is halogen, and, if desired, alkylating the product.

3. A process as claimed in Claim 2 for preparing a compound of formula (III):

\[
\begin{align*}
\text{III} & \quad \text{(III)} \\
R^6\text{OCH}_2 & \quad \text{R^9} \\
\text{HO} & \quad \text{F} \\
\text{F} & \quad \text{F}
\end{align*}
\]

in which:
- $R^6$ is hydrogen or $C_1$-$C_4$ alkyl; and
- $R^9$ is

or a pharmaceutically-acceptable salt thereof.

4. A process as claimed in any one of Claims 1 to 3 for preparing:
- 1-(2-chloro-6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose;
- 1-(2,6-diamino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose;
- 1-(2,6-dioxy-1H,3H,9H-purin-9-yl)-2-desoxy-2,2-difluororibose; or a pharmaceutically-acceptable salt thereof.

5. A compound of formula (II) or (III), or a pharmaceutically acceptable salt thereof, whenever prepared according to a process as claimed in any one of claims 1 to 4.
Patentansprüche

Patentansprüche für folgende Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verwendung einer Verbindung der Formel (I):

   \[
   R^1 \text{OH}_2 C \quad (I)
   \]

   worin
   
   \( R^1 \) Wasserstoff, ein C\textsubscript{1}-C\textsubscript{4}-Alkylrest oder

   \[
   -C-R^5
   \]

   ist;
   \( R^2 \) eine Base ist, die durch eine der folgenden Formeln definiert wird

   \[
   \begin{align*}
   NHR^3 & \quad & O \quad & \quad & \text{X N oder C-R}^4 \text{ ist;} \\
   N-N & \quad & HN\textsuperscript{1} & \quad & R^3\text{HN} \\
   O \quad & \quad & \text{R}^4 & \quad & \text{HN1} \\
   N & \quad & N & \quad & \text{O} \\
   \end{align*}
   \]

   \( R^3 \) Wasserstoff, ein C\textsubscript{1}-C\textsubscript{4}-Alkylrest oder

   \[
   -C-R^5
   \]

   ist;
   \( R^4 \) Wasserstoff, ein C\textsubscript{1}-C\textsubscript{4}-Alkyl-, Aminorest, Brom, Fluor, Chlor oder Iod ist;

   jeder Rest \( R^2 \) unabhängig Wasserstoff oder ein C\textsubscript{1}-C\textsubscript{4}-Alkylrest ist;
oder eines pharmazeutisch annehmbaren Salzes davon, zur Herstellung eines Arzneimittels zur Be- 
handlung empfindlicher Neoplasmen.

2. Verwendung nach Anspruch 1, worin die Verbindung der Formel (I)
\[ \text{1-(4-Amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluorribose,} \]
\[ \text{1-(4-Amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluorxylose,} \]
\[ \text{1-(2,4-Dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluorribose,} \]
\[ \text{1-(4-Amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluorribose} \]
oden ein pharmazeutisch annehmbares Salz davon ist.

3. Verbindung der Formel (II):
\[ \text{(II)} \]

worin
\[ R^1 \text{ Wasserstoff oder ein } C_1-C_4 \text{-Alkylrest ist;} \]
\[ R^2 \text{ eine Ryrimidin-, 5-Aza-pyrimidin oder Purinbase gemäß einer der Formeln} \]

\[ \text{ist;} \]
\[ Q, N, C-(C_2-C_4 \text{-Alkyl}) \text{ oder C-Amino ist;} \]
\[ X, N \text{ oder C-R^3 } \text{ ist;} \]
\[ R^1 \text{ Wasserstoff oder ein } C_1-C_4 \text{-Alkylrest ist;} \]
\[ R^2 \text{ Wasserstoff, ein C-} \text{C}_4 \text{-Alky} \text{lrest, Aminorest, Brom, Fluor, Chlor und iod ist;} \]
oden ein pharmazeutisch annehmbares Salz davon mit dem Vorbehalt, daß \( R^6 \) und \( R^8 \) beide nur dann Wasserstoff sein können, wenn \( X = N \) ist, und weiterhin mit der Maßgabe, daß die Verbindung nicht \( 1-(2\)- 
\[ \text{Amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluorxylose oder 1-(6-Amino-9H-purin-9-yl)-2-desoxy-2,2-} 
\text{difluorxylose ist.} \]

4. Verbindung der Formel (II) nach Anspruch 3 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung für die Chemotherapie eines Säugetieres.
5. Verbindung der Formel (II) oder ein pharmazeutisch annehmbarer Salz davon zur Verwendung für die Behandlung eines empfindlichen Neoplasmas bei einem Säugetier.

6. Pharmazeutisches Präparat zur Verwendung zur Behandlung empfindlicher Neoplasmen bei Säugetieren, umfassend eine Verbindung nach Anspruch 3 oder ein pharmazeutisch annehmbarer Salz davon zusammen mit einem geeigneten pharmazeutisch annehmaren Träger, Verdünnungsmittel oder Hilfsstoff dafür.

7. Verbindung der Formel (III):

![Chemical structure](image)

worin

- $R^6$ Wasserstoff oder ein $C_1$-$C_4$-Alkyrest ist; und
- $R^9$

ist;

oder ein pharmazeutisch annehmbarer Salz davon.

8. Pharmazeutisches Präparat zur Verwendung zur Behandlung empfindlicher Neoplasmen bei Säugetieren, umfassend eine Verbindung nach Anspruch 7 zusammen mit einem geeigneten pharmazeutisch annehmaren Träger, Verdünnungsmittel oder Hilfsstoff dafür.

9. Verbindung der Formel (III) nach Anspruch 7 zur Verwendung für die Chemotherapie eines Säugetieres.

10. Verfahren zur Herstellung einer Verbindung der Formel (II) oder (III) nach Anspruch 3 oder 7, umfassend, daß man die Schutzgruppen eines entsprechend geschützten Nukleosids der Formel (II) oder (III) entfernt.

11. Verfahren zur Herstellung einer Verbindung der Formel (II) oder (III) nach Anspruch 3 oder 7, umfassend, daß man:

   (a) eine Pyrimidinbase der Formel $R^7H$ oder ein geschütztes Derivat davon mit einem Kohlenhydrat der Formel (IV) oder einem geschützten Derivat davon:
kuppelt, worin die Pyrimidinbase $R^7H$ und $R^8$ wie in Anspruch 3 definiert sind und Leav eine
Abgangsgruppe ist und, falls erwünscht, irgendwelche Schutzgruppen, die vorhanden sind, entfernt,
und das Pyrimidinbaseprodukt herzustellen; und
(b) wenn bei einer Verbindung der Formel (III) oder der Formel (II) als Base Purin erwünscht ist, eine
entsprechende Purinnukleosidverbindung, bei der ein C-2- und/oder C-6-Substituent des Purinteils
der Verbindung Halogen ist, mit Ammoniak umsetzt und, falls erwünscht, das Produkt alkyliert.

**Patentansprüche für folgenden Vertragsstaat: AT**

1. Verfahren zur Herstellung einer Verbindung der Formel (II):

   \[
   \text{(II)}
   \]

worin
$R^7$ Wasserstoff oder ein C$_1$-C$_4$-Alkylrest ist;
$R^8$ eine Pyrimidin-, 5-Azapyrimidin- oder Purinbase gemäß einer der Formeln

\[
\begin{align*}
\text{NHR}^8 \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{N}
\end{align*}
\]

ist;
Q N, C$_2$-(C$_2$-C$_4$-Alkyl) oder C-Amino ist;
X N oder C-$R^8$ ist;
$R^7$ Wasserstoff oder ein C$_1$-C$_4$-Alkylrest ist;
$R^8$ Wasserstoff, ein C$_2$-C$_4$-Alkyl-, Aminorest, Brom, Fluor, Chlor und Lodo ist;
od eines pharmazeutisch annehmbaren Salzes davon mit dem Vorbehalt, daß $R^7$ und $R^8$ beide nur
dann Wasserstoff sein können, wenn X N ist, und weiterhin mit der Maßgabe, daß die Verbindung nicht 1-(2-Amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluoroxyllose oder 1-(6-Amino-9H-purin-9-yl)-2-desoxy-2,2-difluoroxyllose ist,

umfassend, daß man die Schutzgruppen eines entsprechend geschützten Nukleosids der Formel (II) entfernt.

2. Verfahren zur Herstellung einer Verbindung der Formel (II): worin

\[ \text{(II)} \]

\[ R^5 \text{ Wasserstoff oder ein } C_1 - C_4 \text{-Alkylrest ist;} \]
\[ R^7 \text{ eine Pyrimidin-, 5-Azapyrimidin- oder Purinbase gemäß einer der Formeln} \]

ist;
\[ Q \text{ N, C-}(C_2 - C_4 \text{-Alky}) \text{ oder C-Amino ist;} \]
\[ X \text{ N oder C-R}^6 \text{ ist;} \]
\[ R^6 \text{ Wasserstoff oder ein } C_1 - C_4 \text{-Alkylrest ist;} \]
\[ R^8 \text{ Wasserstoff, ein } C_1 - C_4 \text{-Alkyl-, Aminorest, Brom, Fluor, Chlor und Iod ist;} \]
or eines pharmazeutisch annehmbaren Salzes davon mit dem Vorbehalt, daß \( R^6 \) und \( R^8 \) beide nur dann Wasserstoff sein können, wenn X N ist, und weiterhin mit der Maßgabe, daß die Verbindung nicht 1-(2-Amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluoroxyllose oder 1-(6-Amino-9H-purin-9-yl)-2-desoxy-2,2-difluoroxyllose ist,

umfassend, daß man

(a) eine Pyrimidinbase der Formel R' H oder ein geschütztes Derivat davon mit einem Kohlenhydrat
der Formel (IV) oder einem geschützten Derivat davon:
kuppelt, worin die Pyrimidinbase $R^7$ H und $R^8$ wie oben definiert sind und Leav eine Abgangsgruppe ist und, falls erwünscht, irgendwelche Schutzgruppen, die vorhanden sind, entfernt, um das Pyrimidinbaseprodukt herzustellen; und
(b) wenn bei einer Verbindung der Formel (III) oder der Formel (II) als Base Purin erwünscht ist, eine entsprechende Purinnucleosidverbindung, bei der ein C-2- und/oder C-6-Substituent des Purinteils der Verbindung Halogen ist, mit Ammoniak umgesetzt und, falls erwünscht, das Produkt alkyliert.

3. Verfahren nach Anspruch 2 zur Herstellung einer Verbindung der Formel (III):

worin
$R^7$ Wasserstoff oder ein $C_1$-$C_4$-Alkylrest ist und
$R^8$ ist,

oder ein pharmazeutisch annehmbares Salz davon.

4. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung von:
1-(2-Chlor-6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluorribose,
1-(2,6-Diamino-9H-purin-9-yl)-2-desoxy-2,2-difluorribose,
1-(2,6-nitrox-1H,3H,9H-purin-9-yl)-2-desoxy-2,2-difluorribose,
oder einem pharmazeutisch annehmbaren Salz davon.

5. Verbindung der Formel (II) oder (III) oder ein pharmazeutisch annehmbares Salz davon, hergestellt nach einem Verfahren nach einem der Ansprüche 1 bis 4.
Revisions
Revisions pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation d'un composé de formule (I):

\[
\begin{align*}
\text{R}^1 & \text{ représente un atome d'hydrogène, un radical alkyle en C}_1-\text{C}_4 \text{ ou} \\
\text{R}^2 & \text{ est une base définie par l'une des formules}
\end{align*}
\]

\[
\begin{align*}
\text{X} & \text{ représente un atome d'azote ou C-R}^4; \\
\text{R}^3 & \text{ représente un atome d'hydrogène, un groupe alkyle en C}_1-\text{C}_4 \text{ ou}
\end{align*}
\]

\[
\begin{align*}
\text{R}^4 & \text{ représente un atome d'hydrogène, un groupe alkyle en C}_1-\text{C}_4, \text{ ou un groupe amino, bromo, fluoro,} \\
& \text{ chloro ou iodo; chaque R}^5 \text{ représente indépendamment un atome d'hydrogène ou un groupe alkyle en} \\
& \text{ C}_1-\text{C}_4; \text{ ou}
\end{align*}
\]
un sel pharmaceutiquement acceptable de ceux-ci, pour la fabrication d’un médicament pour le traitement des tumeurs néoplasiques susceptibles.

2. Utilisation selon la revendication 1 dans laquelle le composé de formule (I) est le 1-(4-amino-2-oxo-1H-pyrimidine-1-y1e)-2-désoxy-2,2-difluoroxyllose, le 1-(4-amino-2-oxo-1H-pyrimidine-1-y1e)-2-désoxy-2,2-difluoroxyllose, le 1-(2,4-dioxy-1H,3H-pyrimidine-1-y1e)-2-désoxy-2,2-difluororibose, le 1-(4-amino-5-méthyl-2-oxo-1H-pyrimidine-1-y1e)-2-désoxy-2,2-difluororibose, ou un sel pharmaceutiquement acceptable de ceux-ci.

3. Composé de la formule (II)

\[
\begin{align*}
\text{II} & \\
\text{R}^6 & = \text{R}^7 = \text{R}^8 \\
\text{H} & = \text{H} & \text{F} & = \text{F} \\
\text{N} & = \text{N} & \text{O} & = \text{O} \\
\text{H} & = \text{H} & \text{H} & = \text{H} \\
\end{align*}
\]

dans laquelle
- \( R^6 \) représente un atome d’hydrogène ou un groupe alkyle en C1-C4 ;
- \( R^7 \) représente une base pyrimidine, 5-aza-pyrimidine ou purine selon l’une des formules
dans lesquelles
- \( Q \) représente un atome d’azote, un groupe C-(C2-C4 alkyle) ou C-amino
- \( X \) représente un atome d’azote ou un groupe C-R^6 ;
- \( R^6 \) représente un atome d’hydrogène ou un groupe alkyle en C1-C4 ;
- \( R^7 \) représente de l’hydrogène, un groupe alkyle en C1-C4 ou un groupe amino, bromo, fluoro, chloro et iodo ; ou
un sel pharmaceutiquement acceptable de celles-ci avec, pour condition, que \( R^6 \) et \( R^8 \) ne peuvent être tous deux de l’hydrogène que si \( X \) représente N et avec comme condition supplémentaire que le composé n’est pas du 1-(2-amino-6-oxo-1H,9H-purine-9-y1e)-2-désoxy-2,2-difluoroxyllose ou du 1-(6-amino-9H-purine-9-y1e)-2-désoxy-2,2-difluoroxyllose.
4. Composé de formule (II) tel que défini dans la revendication 3 ou un sel pharmaceutiquement acceptable de celui-ci, à utiliser pour la chimiothérapie d'un mammifère.

5. Composé de formule (II), ou un sel pharmaceutiquement acceptable de celui-ci, à utiliser pour le traitement des tumeurs néoplasiques susceptibles chez un mammifère.

6. Formulation pharmaceutique à utiliser pour le traitement des tumeurs néoplasiques susceptibles chez les mammifères, comprenant un composé de la revendication 3 ou un sel pharmaceutiquement acceptable de celui-ci, en combinaison avec un support, un diluant ou un excipient pharmaceutiquement acceptable de celui-ci.

7. Composé de la formule (III)

\[
\text{(III)}
\]

dans laquelle
\( R^1 \) représente un atome d'hydrogène ou un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>;
\( R^2 \) représente

8. Formulation pharmaceutique à utiliser pour le traitement des tumeurs néoplasiques susceptibles chez les mammifères, comprenant un composé selon la revendication 7, en combinaison avec un support, un diluant ou un excipient pharmaceutiquement acceptable pour celui-ci.

9. Composé de formule (III) tel que défini à la revendication 7, à utiliser pour la chimiothérapie chez un mammifère.

10. Procédé de préparation d'un composé de formule (II) ou (III), tel que défini à la revendication 3 ou 7, comprenant l'élimination des groupes protecteurs d'un nucléoside protégé de manière correspondante et répondant à la formule (II) ou (III).

11. Procédé de préparation d'un composé de formule (II) ou (III) tel que défini aux revendications 3 ou 7, qui comprend les étapes suivantes:
(a) coupler une base de pyrimidine de formule R'<H ou un dérivé protégé de celle-ci à un hydrate de carbone de formule IV, ou à un dérivé protégé de celui-ci:
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II

R^8\text{CH}_2\text{(sort)}

O

CH-(sort)

f

(IV)

dans laquelle la base pyrimidine R^7H et R^6 sont telles que définies ci-dessus et Sort représente un groupe sortant et, si on le souhaite, l'élimination de tout groupe protecteur présent afin d'obtenir la base pyrimide recherchée; et
(b) si l'on souhaite un composé de formule (III) ou de formule (II) dans lequel la base est une purine, faire réagir avec de l'ammoniaque un composé nucléoside de purine correspondant dans lequel un substituant C-2 et/ou C-6 de la fraction purine du composé est un halogène et, si on le désire, alkyler le produit.

Revendications pour l'Etat contractant suivant : AT

1. Procédé de préparation d'un composé de formule (II)

III

R^8\text{CH}_2\text{C}

O

R^7

(II)

dans laquelle
R^8 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4;
R^7 représente une base pyrimidine ou purine selon l'une des formules
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dans lesquelles
Q représente un atome d'azote, un groupe C-(C₂-C₄ alkyle) ou C-amino
X représente un atome d'azote ou un groupe C-Rⁱ;
Rᵦ représente un atome d'hydrogène ou un groupe alkyle en C₃-C₄;
Rᵢ représente de l'hydrogène, un groupe alkyle en C₁-C₄ ou un groupe amino, bromo, fluoro, chloro et iodo; ou
un sel pharmaceutiquement acceptable de celles-ci avec, pour condition, que Rᵦ et Rᵢ ne peuvent être
tous deux de l'hydrogène que si X représente N et avec comme condition supplémentaire que le
composé n'est pas du 1-(2-amino-6-oxo-1H,9H-purine-9-yle)-2-désoxy-2,2-difluoroxylose ou du 1-(6-
amino-9H-purine-9-yle)-2-désoxy-2,2-difluoroxylose, qui comprend l'élimination des groupes protecteurs
d'un nucléoside protégé de manière correspondante de la formule (II).

2. Procédé de préparation d'un composé de formule (II)

dans laquelle
Rᵦ représente un atome d'hydrogène ou un alkyle en C₁-C₄;
Rᵦ représente une base pyrimidine, 5-aza-pyrimidine ou purine selon l'une des formules
Q représente un atome d’azote, un groupe C-(C₂-C₄ alkyle) ou C-amino;
X représente un atome d’azote ou un groupe C-R⁶;
R⁵ représente un atome d’hydrogène ou un groupe alkyle en C₁-C₄;
R⁶ représente de l’hydrogène, un groupe alkyle en C₁-C₄ ou un groupe amino, bromo, fluoro, chloro et iodo; ou
un sel pharmaceutiquement acceptable de celui-ci avec, pour condition, que R⁵ et R⁶ ne peuvent être tous deux de l’hydrogène que si X représente un atome d’azote et avec comme condition supplémentaire que le composé n’est pas du 1-(2-amino-6-oxo-1H,9H-purine-9-yle)-2-désoxy-2,2-difluoroxylose ou du 1-(6-amino-9H-purine-9-yle)-2-désoxy-2,2-difluoroxylose qui comprend:
(a) coupler une base de pyrimidine de la formule R⁷H ou un dérivé protégé de celle-ci à un hydrate de carbone de la formule IV, ou à un dérivé protégé de celui-ci:

\[ R^6\text{CH}_2\text{O} \quad (\text{sort}) \quad (\text{IV}) \]

dans laquelle la base pyrimidine R⁷H et R⁶ sont tels que définis ci-dessus et Sort représente un groupe sortant et, si on le souhaite, l’élimination de tout groupe protecteur présent pour d’obtenir la base pyrimidine recherchée; et
(b) si l'on souhaite un composé de formule (III) ou de formule (II) dans lequel la base est une purine, faire réagir avec de l'ammoniaque un composé nucléoside de purine correspondant dans lequel un substituant C-2 et/ou C-6 de la fraction purine du composé est un halogène et, si on le désire, alkyler le produit.

3. Procédé selon la revendication 2, pour la préparation d'un composé de la formule (III)

\[
\begin{align*}
R^8 & \text{HoC} \\
& \text{O} \\
& \text{R}^9
\end{align*}
\]

III

dans laquelle
\(R^6\) est un atome d'hydrogène ou un alkyle en C1-C4; et \(R^9\) représente

\[
\begin{align*}
& \text{O} \\
& \text{R}
\end{align*}
\]

ou ou un sel pharmaceutiquement acceptable de celui-ci.


5. Composé de formule (II) ou (III), ou sel pharmaceutiquement acceptable de celui-ci, préparé selon le procédé revendiqué par l'une quelconque des revendications 1 à 4.