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| (54) Title: DESOXYURIDINE DERIVATIVES, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS |
| (57) Abstract |

Desoxyuridine derivatives such as 1-(2-desoxy-β-D-erythropentofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione which derivatives are useful as chemotherapeutical agents particularly in combatting Herpes diseases and infections.
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Desoxyuridine derivatives, processes for their preparation and their use as pharmaceuticals

The present invention concerns desoxyuridine derivatives, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals in particular as viricides in particular against Herpes viruses.

More particularly the invention concerns compounds of formula I

wherein

R₁ and R₂ represent independently hydrogen or lower alkyl,
R₃ represents halogen, CHF₂ or CF₃,
R₄ represents hydrogen, hydroxy or fluorine,
X represents hydrogen, hydroxy or fluorine,
n is 0 or 1,

whereby the sugar radical is α- or β-glycosically bound to the pyrimidine ring;
in free form or acid addition salt form.

The compounds of the invention can be prepared according to the invention
a) by reacting a compound of formula II

\[
\begin{array}{c}
\text{II} \\
\text{HN} \quad \text{C}-(\text{CH}_2)_n-\text{R}_3 \\
\text{OH} \\
\end{array}
\]

with a compound of formula III

\[
\begin{array}{c}
\text{III} \\
\text{HO} \\
\text{OH} \\
\end{array}
\]

or

b) by replacing the group \( R_3' \) in the hydroxalkyl side chain

5 of a compound of formula Ia

\[
\begin{array}{c}
\text{Ia} \\
\text{HN} \quad \text{C}-(\text{CH}_2)_n-\text{R}_3' \\
\text{OH} \\
\end{array}
\]

by an \( R_3 \) group whereby in the formulae Ia, II and III, \( R_1, R_2, R_3, R_4, X \) and \( n \) are as defined above, \( R_5 \) represents halogen or acyloxy, \( R_3' \) represents hydroxy in free or protected form and any hydroxy group present in the sugar radical may be protected;

10 and when required removing any protecting group from the compound thus obtained;

and recovering the compound thus obtained in free form or in acid addition salt form.

Process a) can be carried out for example by converting a

15 compound of formula II in conventional manner into its trimethylsilyl derivative and reacting this with a compound of formula III whose hydroxy groups are protected in a solvent e.g. a halogenated hydrocarbon or acetonitrile.
According to process b) a compound of formula Ia in unprotected or protected form can be dissolved in a solvent inert under the reaction conditions e.g. a lower alky1 carboxylic acid amide such as dimethylformamide.

5 The conversion of \( R_3' \) to halogen can be carried out either with free or with protected OH-groups in the sugar moiety.

When \( R_3 \) represents halogen the reaction can be carried out using a conventional halogenation method e.g. employing carbon tetrachloride or bromosuccinimide. When \( R_3 \) represents CHF\(_2\) or CF\(_3\) the reaction can be carried out using conventional fluorination methods e.g. from a compound of formula Ia after oxidation to an aldehyde with a dialkylsulfurtrifluoride or after oxidation to a carboxylic acid, with a sulphur tetrafluoride.

Examples of protecting groups are those conventionally employed in reactions of this nature such as p-tolyl, benzyl, p-nitrobenzoyl, trimethylsilyl. These can be introduced and removed using conventional procedures.

Salt forms can be prepared in conventional manner from free forms and vice versa.

20 As stated above, the compounds of formula I and Ia can be in \( \alpha- \) or \( \beta- \) configuration with respect to bonding of the sugar radical. Merely for convenience the compound of formula I is shown in \( \beta- \) form.

The pyrimidine radical in the compounds of formula I and Ia can exist in tautomeric forms such as

\[
\begin{align*}
\text{HN} & \hspace{1cm} \text{HN} \\
\text{O/NH} & \hspace{1cm} \text{O/NH} \\
\text{ONH} & \hspace{1cm} \text{ONH}
\end{align*}
\]

25 The invention is intended to cover all tautomeric forms of the compounds.

The compounds of formula I and Ia can also exist in the form of optical isomers or mixtures which isomers can be separated in conven-
tional manner. The invention is intended to cover isomeric forms and mixtures thereof, whereby the compounds are present in the latter form unless otherwise mentioned.

Lower alkyl groups contain 1 to 4 preferably 1 or 2 carbon atoms.

The starting materials of formula Ia are also new and form part of the invention. They can be prepared by reacting a compound of formula IIa

\[
\begin{align*}
\text{HN} & \quad \text{C} - (\text{CH}_2)_n - \text{R}_3' \\
\text{O} & \quad \text{R}_2
\end{align*}
\]

wherein \( \text{R}_1, \text{R}_2, \text{R}_3', \text{X} \) and \( n \) are as defined above analogously to process a) with a compound of formula III

The compounds of formula II, IIa and III are either known or can be prepared analogously to known methods e.g. as illustrated hereinafter in the examples.

End products and intermediates can be isolated and purified in conventional manner.

The compounds of formula I exhibit chemotherapeutic, in particular anti-viral agents as indicated in particular by their effect against Herpes viruses which can be demonstrated in vitro and in vivo, for example by the reduction of cytopathogenic effects (CPE) of various viruses e.g. Herpes simplex I and II in vitro from concentration of ca. 0.003 \( \mu \text{g/ml} \) to ca. 300 \( \mu \text{g/ml} \) and in vivo in tests carried out in mice and guinea pig using systemic, topical and encephalitis-infection models (cf. H.E. Renis et al. J. Med. Chem. 16(7) 754 [1973]). The compounds are therefore useful as chemotherapeutics in particular as agents for combating Herpes diseases and infections.
For this use a suitable daily dosage is from about 200 to 1200 mg suitably given in divided doses two to four times a day containing about 50 to 600 mg of the compounds or in retard form.

Compounds can be employed in free form or, when the compound is sufficiently basic, also in the form of a chemotherapeutically acceptable acid addition salt thereof, especially when X is imino, which forms have the same order of activity as the free forms. Suitable salt forms include hydrochloride, hydrogenfumarate and naphthalene-1,5-disulfonate.

Compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and administered in such forms as tablets or capsules or parenterally. Such compositions also form part of the invention.
The invention therefore also concerns a method of combating herpes diseases or infections comprising administering to a subject in need of such treatment an effective amount of a compound of formula I or a chemotherapeutically acceptable acid addition salt thereof and such compounds for use as chemotherapeutic agents, in particular as anti-viral agents especially against herpes viruses.

Examples of particular substituent meanings are

\[ R_1, R_2 = \begin{align*}
  & \text{a) } H \\
  & \text{b) lower alkyl preferably methyl or ethyl} \\
  \end{align*} \]

\[ R_3 = \begin{align*}
  & \text{a) halogen} \\
  & \text{b) chlorine, bromine, iodine} \\
  \end{align*} \]

\[ X = \text{oxygen} \]

\[ n = 1 \]

\[ R_4 = \begin{align*}
  & \text{a) } H, \text{ OH, F} \\
  & \text{b) } H, \text{ OH, especially } H \\
  \end{align*} \]

and combinations of these.

Examples of particular compound groups are thus those of formula I,

\[ \text{a) wherein } R_1 \text{ and } R_2 \text{ represent hydrogen, } R_3 \text{ represents halogen, } R_4 \text{ represents hydrogen, hydroxy or fluorine, } X \text{ represents oxygen or imino and } n \text{ is 1;} \]

\[ \text{b) wherein } R_1 \text{ and } R_2 \text{ are as defined above, } R_3 \text{ represents halogen, } X \text{ represents oxygen, } R_4 \text{ represents hydrogen, hydroxy or fluorine and } n \text{ is 1.} \]

A particularly preferred individual compound is

\[ 1-(2\text{-desoxy-β-D-erythro-pentofuranosyl})-5-(2\text{-chloroethyl})-(1H,3H)-pyrimidine-2,4-dione \]

in free form or acid addition salt form.

The following examples illustrate the invention whereby temperatures are given in degrees centigrade.
Example 1: 1-(2-desoxy-β-D-erythro-pentofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione (Process b):

200 mg of 1-(2-desoxy-β-D-erythro-pentofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione and 400 mg of triphenylphosphine are dissolved in 20 ml of abs. dimethylformamide reacted with 0.2 ml of carbon tetrachloride and 0.2 ml of abs. pyridine and left standing for 1 hour at room temperature. The solvent is then removed in vacuum with addition of 1-butanol, chromatographed on a silica gel column (chloroform/methanol = 9/1) to obtain the title compound as colourless crystals m.p. 166-67° (from abs. methanol).

Example 2: 1-(2-desoxy-α-D-erythro-pentofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione (Process b):

1.5 g of 1-(2-desoxy)-3,5-di-O-p-toluyl-α-D-erythro-pentofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione are dissolved in 20 ml of abs. dimethylformamide, reacted with 2.3 g of triphenylphosphine, 1 ml of abs. carbon tetrachloride and 0.5 ml of abs. pyridine and maintained for 10 minutes at 70°. The solvent is then removed at 0.1 bar and the remaining syrup chromatographed on silica-gel (toluene/ethylacetate = 2/1). 0.5 g of 1-(2-desoxy-3,5-di-O-p-toluyl-α-D-erythro-pentofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione are obtained as colourless crystals (m.p. 142-144°). To remove the p-toluyl groups the compound is dissolved in 10 ml of abs. ethanol and reacted with 1.5 ml of 1N-sodium ethanolate solution in ethanol, left for 15 minutes at room temperature and reacted with 1.5 ml of 1N acetic acid. The solvent is removed in vacuum and the remaining syrup treated with diethylether/water. Chromatography of the aqueous phase on silica-gel (chloroform/methane = 9/1) yields the title compound as colourless crystals m.p. 140-142° (ethanol/chloroform).
Example 3: \(1-(2\text{-desoxy-\(\beta\)-D-erythro-pentofuranosyl})-5-(2\text{-bromoethyl-}
(1H,3H)-\text{pyrimidine-2,4-dione})\) (Process b):

1.14 g of \(1-(2\text{-desoxy-\(\beta\)-D-erythro-pentofuranosyl})-5-(2\text{-hydroxy-
ethyl})-(1H,3H)-\text{pyrimidine-2,4-dione}\) are dissolved in 30 ml of abs.
dimethylformamide, reacted with 2.3 g of triphenylphosphine and 1.2 g of
N-bromosuccinimide and kept for 90 minutes at room temperature.
The solvent is removed in vacuum and evaporation repeated following
addition of n-butanol. A yellow syrup is obtained which, after
crystallisation from ethanol/chloroform, yields the title compound
as colourless crystals m.p. 161-163°.

Example 4: \(1-(2\text{-desoxy-\(\alpha\)-D-erythro-pentofuranosyl})-5-(2\text{-bromoethyl-}
(1H,3H)-\text{pyrimidine-2,4-dione})\) (Process b):

380 mg of \(1-(2\text{-desoxy-\(\alpha\)-D-erythro-pentofuranosyl})-5-(2\text{-hydroxy-
ethyl})-(1H,3H)-\text{pyrimidine-2,4-dione}\) are reacted analogously to
Example 3 to yield the title product m.p. 131-133° (ethanol/chloroform).

Example 5: \(1-(2\text{-desoxy-\(\beta\)-D-erythro-pentofuranosyl})-5-(2\text{-iodoethyl-}
(1H,3H)-\text{pyrimidine-2,4-dione})\) (Process b):

550 mg of \(1-(2\text{-desoxy-\(\beta\)-D-erythro-pentofuranosyl})-5-(2\text{-hydroxy-
ethyl})-(1H,3H)-\text{pyrimidine-2,4-dione}\) and 1.1 g of triphenylphosphine
are dissolved in 25 ml of abs. dimethylformamide, reacted with
550 mg of N-bromosuccinimide and 3.3 g of tetrabutylammonium iodide
and kept for 90 minutes at room temperature. The solvent is then
removed, after addition of n-butanol, in vacuum and the residue
chromatographed on silica-gel (chloroform/methanol = 9/1) to obtain
the title compound m.p. 160-161°.
Example 6: 1-(2-desoxy-β-D-erythro-pentofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione (Process a):

480 mg of 5-(2-chloroethyl)uracil are suspended in hexamethyl-disalazane, reacted with 0.3 ml of trimethylcholorosilane and refluxed for 3 hours. Volatile matter is then removed in vacuum and evaporation repeated twice after addition of abs. xylene. The remaining syrup is dissolved in 30 ml of abs. chloroform and reacted at room temperature with 1.2 g of 3,5-di-o-p-tolyl-2-desoxy-D-erythro-pentofuranosyl-chloride and then with 0.5 ml of trifluoro-methanesulfonic acid trimethylsilylester. The mixture is kept for 30 minutes at room temperature and then shaken with 1.5 ml of cold saturated aqueous KHC0₃. Concentration of the organic phase in vacuum yields a syrup which is chromatographed on silica-gel (toluene/ethyl acetate = 4/1) to yield 1-(2-desoxy-3,5-di-o-p-tolyl-β-D-erythro-pentofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione (m.p. 167-169°). Removal of the p-tolyl groups is carried out analogously to Example 2 to yield 1-(2-desoxy-β-D-erythropentofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione as colourless crystals m.p. 165-166° (from water).

Example 7: 1-(β-D-arabinofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione (Process b):

400 mg of 1-(β-D-arabinofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione are dissolved in 10 ml of abs. dimethylformamide, reacted with 0.7 g of triphenylphosphine, 0.3 ml of carbon tetrachloride and 0.3 ml of pyridine and kept for 1.5 hours at room temperature. Following addition of 1-butanol the mixture is evaporated to dryness on a Rotavapor and the syrupy residue chromatographed on silica-gel (chloroform/methanol = 8/1). Concentration of the appropriate fractions gives the title compound as colourless crystals m.p. 182-183° (from ethanol).
Example 8: 1-(β-D-arabinofuranosyl)-5-(2-bromoethyl)-(1H,3H)-pyrimidine-2,4-dione

320 mg of 1-(β-D-arabinofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione are dissolved in 5 ml of abs. dimethylformamide, reacted with 650 mg of triphenylphosphine and 300 mg of N-bromosuccinimide and kept a room temperature for 1.5 hours. Following addition of 5 ml of 1-butanol the mixture is concentrated to dryness on a Rotavapor and the supyr residue chromatographed on silica-gel (chloroform/methanol = 6/1). Concentration of the fractions yields the title compound as colourless crystals m.p. 166-167° (from acetone/chloroform).

Example 9: 1-(2-desoxy-2-fluoro-β-D-arabinofuranosyl)-5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione

200 mg of 1-(2-desoxy-2-fluoro-β-D-arabinofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione are dissolved in 5 ml of abs. dimethylformamide and reacted with 300 mg of triphenylphosphine and 0.3 ml of a 1:1 mixture of abs. pyridine and carbon tetrachloride. The mixture is stirred for 4 hours at room temperature, 10 ml 1-butanol added and the mixture concentrated to dryness on an oil pump. The residue is chromatographed on silica-gel (chloroform/methanol = 9/1). Concentration of the fractions yields the title compound as a highly hygroscopic colourless powder.

Example 10: 4-amino-5-(2-chloroethyl)-1-(2-desoxy-β-D-erythrobifuranosyl)-1H-pyrimidine-2-one

3.12 g of a 4-amino-5-(2-hydroxyethyl)-1H-pyrimidine-2-one are sylated analogously to Example 6 and reacted with 7.76 g of 2-desoxy-3,5-di-O-p-toluoyl-D-erythro-pentofuranosyl-chloride. After shaking with 100 ml of saturated aqueous KHC0₃ the chloroform is removed in vacuum and the residue chromatographed on silica-gel (chloroform/methanol = 9/1) to yield 4-amino-1-(2-desoxy-3,5-di-O-p-toluoyl-D-erythro-pentofuranosyl)-
5-(2-hydroxyethyl)-1H-pyrimidine-2-one. 1.4 g of this anomic mixture are stirred in 20 ml of dimethylformamide with 1.4 g of triphenylphosphine, 0.6 ml of abs. carbon tetrachloride and 0.6 ml of abs. pyridine for 2 hours at room temperature. After addition of 10 ml of 1-butanol the solvents are removed in vacuum and the residue mixed with 20 ml of methanol and 5 ml of 1N methanolic sodium methanolate. On completion of reaction the mixture is neutralised with 1N acetic acid and evaporated in vacuum. Treatment of the residue with 30 ml of ethylacetate and 10 ml of methanol yields the title compound as colourless crystals m.p. 174° (from water).

The required starting materials may be prepared for example as follows:

A) 1-(2-desoxy-β-D-erythro-pentofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione (for examples 1, 3, 5):

10.5 g of 5-(2-hydroxyethyl)-uracil are suspended in 60 ml of hexamethyldisilazane, reacted with 3 ml of trimethylchlorosilane and refluxed for 2 hours. All volatile material is removed in vacuum and evaporation repeated twice after addition of abs. xylene. The remaining syrup is dissolved in 400 ml of abs. chloroform and reacted at room temperature with 26.2 g of 3,5-di-O-p-tolyl-2-desoxy-D-erythro-pentofuranosyl-chloride and then with 0.5 ml of trifluoromethanesulfonic acid trimethylsilylester. The mixture is kept at room temperature for 1 hour and shaken with 100 ml saturated aqueous KHCO₃. Concentration of the organic phase in vacuum yields a yellow syrup which is crystallised to give 5-(2-hydroxyethyl)-3',5'-di-O-p-tolyl-β-D-2'-desoxyuridine (m.p. 176-178°). Removal of the p-toluyl groups is carried out analogously to Example 2 to yield, after crystallisation from ethanol in a refrigerator, 1-(2-desoxy-β-D-erythro-pentofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione as colourless crystals, m.p. 160-161°.
8) 1-(2-deoxy-3,5-di-O-p-tolyl-α-D-erythro-pentofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione (for Example 2):

Using 5-(2-hydroxyethyl)-uracil and 3,5-di-O-p-tolyl-2-deoxy-D-ribofuranosylchloride and proceeding analogously to A) there is obtained following fractional crystallisation from ethanol the title compound.

C) 1-(2-deoxy-α-D-erythro-pentofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione (for Example 4):

Obtained after removal of tolyl groups analogously to Example 2 and chromatographed on silica-gel (chloroform/methanol = 3/1). Colourless oil.

D) 5-(2-chloroethyl)-(1H,3H)-pyrimidine-2,4-dione (for example 6):

0.5 g of 5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione are dissolved in 20 ml of abs. dimethylformamide and 2.5 g of triphenylphosphine, 30 ml of carbon tetrachloride and 1 ml pyridine added. The solution is kept for 1.5 hours at 80°, concentrated and the oily residue taken up in chloroform/methanol (9/1) to yield the title compound as colourless crystals, m.p. 260-262° (from ethylacetate).

E) 1-(β-D-arabinofuranosyl)-5-(2-hydroxyethyl)-(1H,3H)-pyrimidine-2,4-dione (for examples 7 and 8)

5 g of 2,3,5-tri-O-benzyl-1-O-p-nitrobenzoyl-D-arabinose are dissolved in 80 ml of abs. dichloromethane, which had been saturated 1 hour previously at 0° with HCl. Stirring is carried out for 2 hours at 0° with passage of further HCl and the precipitated p-nitrobenzoic acid removed. The filtrate is concentrated to dryness and the oily residue left for a further 2 hours on a Rotavapor at 0.0013 bar. The residue is dissolved in abs. dichloromethane, reacted with a syrup containing hexamethyilsilazane-free silated 5-(2-hydroxyethyl)-uracil
[prepared from 2.93 g of 5-(2-hydroxyethyl)-uracil (analogously to A)]
and shaken in the presence of 10 g molecular sieve (4 Å), for 2 days
at room temperature. After filtration and washing of the molecular
sieve the filtrate is shaken with cold saturated aqueous KHCO₃,
the aqueous phase washed once with dichloromethane and the combined
organic phases concentrated on a Rotavapor to give a partially
crystalline syrup. 1 g of PdCl₂ is suspended in 150 ml of methanol
and hydrogenated on a PARR-apparatus to Pd (H₂, room temperature at
4 atmospheres, ca. 30 minutes). To this is added the above syrup
dissolved in 100 ml of methanol and the mixture hydrogenated over-
night at 4 atmospheres with H₂. A white crystalline precipitate is
formed in the hydrogenation vessel, further product is in solution.
The precipitate and the Pd are filtered off the product
dissolved in water and filtered off from the Pd, the
filtrate concentrated on a Rotavapor and the residue recrystallised
from water. The methanolic residue of the hydrogenation is neutralised
with ion-exchanger Merck II (strongly basic), filtered over active
carbon, concentrated and the crystalline residue recrystallised from
water. The title product is obtained as colourless needles m.p.212-15°.

1-(2-desoxy-2-fluoro-ß-D-arabinofuranosyl)-5-(2-hydroxyethyl)-
(1H,3H)-pyrimidine-2,4-dione (for example 9):

3.1 g of 5-(2-acetoxyethyl)-uracil are silated analogously to
A) and after working-up reacted with 4 g of 3-O-acetyl-5-O-benzoyl-2-
desoxy-2-fluoro-D-arabinofuranosylbromide in abs. dichloromethane.
After 14 days the mixture is worked up by addition of a few ml of
methanol, filtration, and column separation (chloroform/methanol =
9/1). After removal of the protecting groups (cf. Example 2) the title
compound is obtained as colourless crystals, m.p. 177-178°.
NMR-Spectra

KH = imprecisely assigned proton in desoxyribose moiety
KH-1'α, KH-1'β = proton on C-1 of desoxyribose moiety, the bonding properties of which allow assignment of anomers.

NMR-Apparatus: Bruker WH-90, 90 MHz.

5 Example Spectrum

1

2.10 (t, 2H, KH); 2.67 (t, 2H, CH₂CH₂Cl, J = 7 Hz); 3.4-3.9 (m, 5H, CH₂CH₂Cl, KH); 4.1-4.4 (m, 1H, KH); 5.03 (t, 1H, J = 5.1 Hz, 5'-OH); 5.24 (d, 1H, J = 4.3 Hz, 3'-OH); 6.17 (t, 1H, J = 6.7 Hz, KH-1'β); 7.83 (s, 1H, H-6); 11.4 (br, 1H, NH).

2

1.8-2.7 (m, 2H, KH); 2.66 (t, 2H, J = 7 Hz, CH₂CH₂Cl); 3.43 (d, 2H, KH); 3.69 (t, 2H, J = 7 Hz, CH₂CH₂Cl); 4.1-4.3 (m, 2H, KH); 4.82 (t, 1H, J = 5.7 Hz, 5'-OH); 5.30 (d, 1H, J = 3.1 Hz, 3'-OH); 6.10 (dubl.d, 1H, J = 7.4 Hz, KH-1'α); 7.85 (s, 1H, H-6); 10.9 (br, 1H, NH).

3

2.14 (t, 2H, KH); 2.79 (t, 2H, J = 7.9 Hz, CH₂CH₂Br); 3.5-4.0 (m, 5H, CH₂CH₂Br, KH); 4.29 (d, 1H, KH); 4.76 (br, 2H, 3'-OH,5'-OH); 6.20 (t, 1H, J = 6.7 Hz, KH-1'β); 7.85 (s, 1H, H-6); 11.4 (s, 1H, NH).

4

1.7-2.5 (m, 2H, KH); 2.71 (t, 2H, J = 7 Hz, CH₂CH₂Br); 3.3-3.5 (m, 2H, KH); 3.53 (t, 2H, J = 7 Hz, CH₂CH₂Br); 4.0-4.3 (m, 2H, KH); 4.80 (t, 1H, J = 5.1 Hz, 5'-OH); 5.27 (d, 1H, J = 3.2 Hz, 3'-OH); 6.07 (dubl.d, 1H, J = 7.5 Hz, KH-1'α); 7.82 (s, 1H, H-6); 11.32 (s, 1H, NH).

5

2.06 (t, 2H, KH); 2.72 (t, 2H, J = 7 Hz, CH₂CH₂J); 3.4-3.9 (m, 5H, CH₂CH₂J, KH); 4.21 (br, 1H, KH); 4.99 (t, 1H, J = 2.5 Hz, 5'-OH); 5.20 (d, 1H, J = 4 Hz, 3'-OH); 6.13 (t, 1H, J = 6.5 Hz, KH-1'β); 7.77 (s, 1H, H-6); 11.35 (s, 1H, NH).
2.66 (t, 2H, J = 7.2 Hz, CH₂CH₂Cl); 3.5-3.8 (m, 5H, CH₂Cl and KH); 3.85-4.1 (m, 2H, KH); 5.0 (t, 1H, J = 5.4 Hz, 5'-OH); 5.36 and 5.45 (je 1d, J = 5 Hz, 2H, 3'-OH and 5'-OH); 6.02 (d, 1H, J = 5.4 Hz, KH-1'B); 7.67 (s, 1H, H-6); 11.32 (s, 1H, NH).

2.75 (t, 2H, J = 7.4 Hz, CH₂CH₂Br); 3.4-3.8 (m, 5H, CH₂Br and KH); 3.85-4.1 (m, 2H, KH); 4.2-5.7 (br, 3H, 2'-OH, 3'-OH, 5'-OH); 6.01 (d, 1H, J = 4.5 Hz, KH-1'B); 7.66 (s, 1H, H-6); 11.32 (s, 1H, NH).

2.7 (t, 2H, J = 7 Hz, CH₂CH₂Cl); 3.5-4.25 (m, 7H, CH₂Cl and KH); 4.25 (dt, 1H, H-3', Jₜ-₅₁-F = 20.45 Hz, Jₜ-H₁ = 4 Hz); 5.05 (dt, 1H, H-2', Jₜ-₅₁-F = 22.2 Hz, Jₜ-H₁ = 4 Hz); 6.1 (dd, 1H, H-1', Jₜ-₅₁-F = 15.3 Hz, Jₜ-H₁ = 4.1 Hz); 7.7 (s, 1H, H-6); 11.55 (s, 1H, NH).

2.0 (m, 2H, KH); 2.8 (t, 2H, J = 7 Hz, CH₂CH₂Cl); 3.5-3.9 (m, 5H, CH₂Cl and KH); 4.2 (br s, 1H, KH); 5.0-5.2 (br s, 2H, 2 OH); 6.2 (t, 1H, J = 7 Hz, KH-1'B); 7.3 (s, 2H, NH₂); 7.8 (s, 1H, H-6).

2.1 (t, 2H, KH); 2.3 (t, 2H, CH₂CH₂OH); 3.3-3.7 (m, 4H, CH₂CH₂OH, KH); 3.7-3.85 (m, 1H, KH); 4.1-4.4 (m, 1H, KH); 4.54 (t, 1H, J = 5 Hz, CH₂CH₂OH); 5.00 (t, 1H, J = 5 Hz, 5'-OH); 5.23 (d, 1H, J = 4.3 Hz, 3'-OH); 6.16 (t, 1H, J = 7 Hz, KH-1'B); 7.68 (s, 1H, H-6); 11-11.5 (br, 1H, NH).

2.1-2.4 (m, 10H, toluyl-CH₂, CH₂CH₂OH, KH); 3.32 (t, 2H, J = 8 Hz, CH₂CH₂OH); 4.3-4.7 (m, 3H, KH, CH₂CH₂OH); 5.02 (m, 1H, KH); 5.56 (d, 1H, KH); 6.23 (dubl.d, 1H, J = 5.5 Hz, KH-1'a); 7.28-7.40 (m, 4H, toluyl); 7.66 (s, 1H, H-6); 7.78-7.98 (m, 4H, toluyl); 11.32 (s, 1H, NH).
1.7-2.5 (m, 2H, KH); 2.31 (t, 2H, J = 7 Hz, CH₂CH₂OH); 3.3 (m, 2H, KH); 4.1 (m, 2H, KH); 4.5 (br s, 1H, OH); 4.8 (br d, 1H, OH); 5.27 (br t, 1H, OH); 6.08 (dd, 1H, KH-1';α); 7.71 (s, 1H, H-6); 11.0 (br s, 1H, NH).

D

2.71 (t, 2H, J = 8 Hz, CH₂CH₂Cl); 3.70 (t, 2H, J = 8 Hz, CH₂Cl); 7.16 (d, 1H, J = 7 Hz, H-6); 10.16 and 10.34 (2 br s, each 1H, 2NH).

E

2.36 (t, J = 6.3 Hz, 2H, CH₂CH₂OH); 3.4-3.8 (m, 5H, CH₂CH₂OH, KH); 3.85-4.1 (m, 2H, KH); 4.46 (t, J = 5.4 Hz, 1H, CH₂CH₂OH); 5.00 (t, J = 5.4 Hz, 1H, 5'-OH); 5.37 and 5.45 (2d, J = 5 Hz, 2H, 2'-OH, 3'-OH); 6.01 (d, J = 4.5 Hz, 1H, KH-1'O); 7.54 (s, 1H, H-6); 11.95 (s, 1H, NH).

F

2.34 (t, 2H, J = 7 Hz, CH₂CH₂OH); 3.3-4.0 (m, 5H, CH₂OH, KH); 4.25 (br dt, 1H, J₁H-3'-F = 22.5 Hz, H-3'); 4.57 (t, 1H, CH₂OH); 5.05 (dt, 1H, J₁H-2'-F = 51.1 Hz, 1H-H = 4 Hz, H-2'); 5.1 (m, 1H, 5'-OH); 5.86 (dd, 1H, J₁H-H = 4 Hz, 3'-OH); 6.1 (dd, 1H, J₁H-1'-F = 16.4 Hz, 1H-H = 4.1 Hz, H-1'); 7.57 (s, 1H, H-6); 11.41 (s, 1H, NH).
We Claim:

1. Compounds of formula I

\[
\begin{align*}
\text{C} & \equiv \text{(CH}_2\text{)}_n\text{-R}_3 \\
\text{R}_1 & \equiv \text{X} \\
\text{R}_2 & \equiv \text{R}_4 \\
\text{R}_4 & \equiv \text{HO} \\
\end{align*}
\]

wherein

- \( R_1 \) and \( R_2 \) represent independently hydrogen or lower alkyl,
- \( R_3 \) represents halogen, CHF_2 or CF_3,
- \( R_4 \) represents hydrogen, hydroxy or fluorine,
- \( X \) represents oxygen or imino, and
- \( n \) is 0 or 1,

whereby the sugar radical is \( \alpha \)- or \( \beta \)-glycosically bound to the pyrimidine ring;

in free form or acid addition salt form.

2. A compound according to Claim 1
   a) wherein \( R_1 \) and \( R_2 \) represent hydrogen, \( R_3 \) represents halogen,
      \( R_4 \) represents hydrogen, hydroxy or fluorine, \( X \) represents oxygen or imino and \( n \) is 1,
      in free form or acid addition salt form.

3. A compound according to Claim 1
   wherein \( R_1 \) and \( R_2 \) are as defined in Claim 1, \( R_3 \) represents halogen, \( X \) represents oxygen, \( R_4 \) represents hydrogen,
   hydroxy or fluorine and \( n \) is 1,
   in free form or acid addition salt form.
4. 1-(2-desoxy-β-D-erythro-pentofuranosyl)-5-(2-chloroethyl)-(1H, 3H)-pyrimidine—2,4-dione.

5. A chemotherapeutical composition comprising a compound according to Claim 1, in free form or chemotherapeutically acceptable acid addition salt form together with a chemotherapeutically acceptable diluent or carrier.

6. A method of combating herpes diseases or infections which comprises administering to a subject in need of such treatment an effective amount of a compound according to Claim 1 in free form or in chemotherapeutically acceptable acid addition salt form.

7. A compound according to Claim 1, in free form or in chemotherapeutically acceptable acid addition salt form for use as a pharmaceutical.

8. A process for preparing a compound of formula I according to Claim 1 in free form or in acid addition salt form

a) by reacting a compound of formula II

\[
\begin{align*}
\text{II} \\
\text{with a compound of formula III}
\end{align*}
\]

or

b) by replacing the group R₃ in the hydroxalkyl side chain of a compound of formula Ia
by an $R_3$ group whereby in the formulae Ia, II and III, $R_1$, $R_2$, $R_3'$, $R_4$, $X$ and $n$ are as defined in Claim 1, $R_5$ represents halogen or acyloxy, $R_3'$ represents hydroxy and any hydroxy group present in the sugar radical may be protected; and when required removing any protecting group from the compound thus obtained; and recovering the compound thus obtained in free form or in acid addition salt form.

9. A compound of formula Ia

10 wherein $R_1$, $R_2$, $R_4$, $X$ and $n$ are as defined in Claim 1, and whereby the sugar radical is $\alpha$- or $\beta$-glycosidally bound to the pyrimidine ring.
IN INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC:\ C 07 H 19/06; A 61 K 31/00

II. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>X</td>
<td>Chemical Abstracts, vol. 90, no. 23, 4 June 1979 (Columbus, Ohio, US) S.Ya. Mel'nik et al.: &quot;Synthesis and study of 5-(polyfluoroalkyl)- and 5-(polyfluoralkoxyalkyl)-2'-deoxypyrimidine nucleosides&quot;, see page 696, abstract no. 187266g, Bioorg. Khim. 1979, 5(1), 41-6 (Russ)</td>
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<td>and Chemical Abstracts Tenth Collective Index Chemical Substances, page 54902cs uridine, 2'-deoxy-5-(3,3,3-trifluoropropyl)-virucidal activity of, page 46589cs 2,4(1H,3H)-</td>
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  "A" document defining the general state of the art which is not considered to be of particular relevance
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"Y", document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search: 8th November 1983
Date of Mailing of the International Search Report: 18 DEC 1983
International Searching Authority: EUROPEAN PATENT OFFICE

Signature of Authorized Officer: G.L.M. Kruydenberg
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<td>Chemical Abstracts, vol. 97, no. 23, 6 December 1982 (Columbus, Ohio, US) S.Y. Mel'nik et al.: &quot;Synthesis of thymidine analogs with branched substitutions at the 5 position of the pyrimidine ring&quot;, see page 608, abstract no. 198501h, Bioorg. Khim. 1982, 8(8), 1102-7 (Russ)</td>
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This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/11/83.

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