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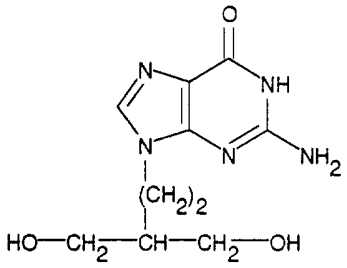
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(54) Virsraksts: **Penciklovira atvasinājumi: hepatīta-B infekciju ārstēšanai**

(57) Kopsavilkums: Savienojumus ar formulu



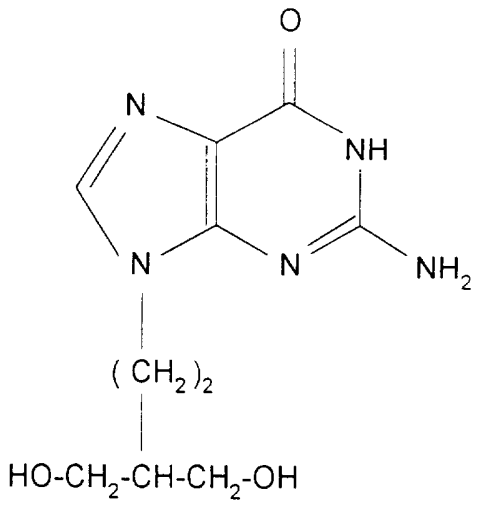
(A)

vai tā farmaceitiski saderīgos sāļus vai atvasinājumus var lietot medikamentu iegūšanai, kurus lieto hepatīta-B vīrusa izraisītās infekcijas ārstēšanai cilvēkiem un dzīvniekiem.

* pieteikums pieņemts ievērojot LR Patentu likuma Pārejas noteikumu 1. punktu
(Eiropas pat. publ. Nr. 0388049, reģistrācijas diena 17.05.1995
Eiropas pat. piet. Nr. 90302186.3, iesniegšanas datums 01.03.1990)

IZGUDROJUMA FORMULA

1. Savienojuma ar formulu (A)



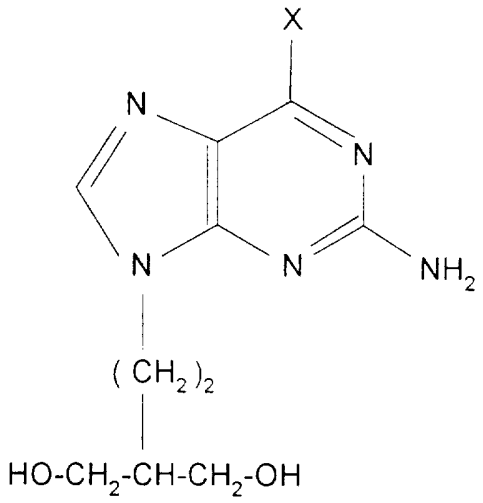
vai tā medikamenta priekšteča, vai farmaceitiski saderīga sāls, fosfāta estera un/vai acilatvasinājuma - jebkura no iepriekšminētajiem - pielietošana medikamenta iegūšanai, kurus lieto hepatīta-B vīrusa infekciju ārstēšanai.

2. Pielietošana saskaņā ar 1. punktu, kas atšķiras ar to, ka šis savienojums ir penciklovīrs ar formulu (A).

3. Pielietošana saskaņā ar 1. punktu, kas atšķiras ar to, ka šis savienojums ir savienojuma ar formulu (A) nātrija sāls hidrāts.

4. Pielietošana saskaņā ar 3. punktu, kas atšķiras ar to, ka medikaments ir ūdenī šķīstošā formā, kas piemērota parenterālai ievadīšanai.

5. Pielietošana saskaņā ar 1. punktu, kas atšķiras ar to, ka savienojums ir savienojuma ar formulu (A) medikamenta priekštecis, kurš atbilst formulai (B)



(B)

vai tā sālim vai atvasinājumam, kā norādīts 1. punktā attiecībā uz formulu (A), kur X ir C_{1-6} alkoksigrupa, NH_2-grupa vai ūdeņraža atoms.

6. Pielietošana saskaņā ar 5. punktu, kas a t š ķ i r a s ar to, ka medikamenta priekštecis ar formulu (B) ir famciklovīrs, kur X ir ūdeņraža atoms un kur divas OH-grupas ir acetilatvasinājuma formā.

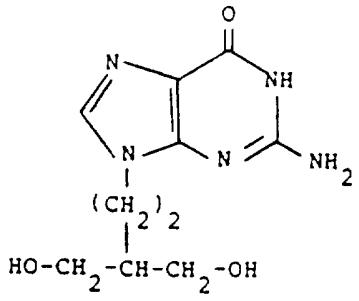
7. Pielietošana saskaņā ar 6. punktu, kas a t š ķ i r a s ar to, ka medikaments ir piemērots orālai ievadīšanai.

8. Pielietošana saskaņā ar 1. punktu, kas a t š ķ i r a s ar to, ka savienojuma vienas devas daudzums, kas tiek ievadīts, ir no 50 mg līdz 1g.

Description

This invention relates to the use of compounds in the preparation of a medicament for use in the treatment of infections caused by hepatitis B virus, in humans and animals.

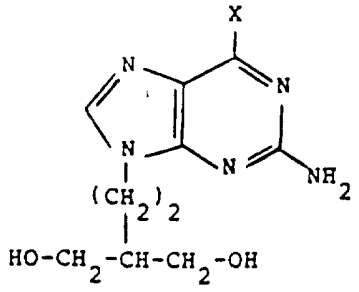
EP-A-141927 (Beecham Group p.l.c) discloses penciclovir, the compound of formula (A):



(A)

and salts, phosphate esters and acyl derivatives thereof, as antiviral agents. The sodium salt hydrate of penciclovir is disclosed in EP-A-216459 (Beecham Group p.l.c.).

Pro-drugs of the compound of formula (A) are of formula (B):



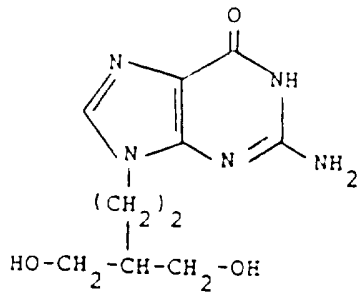
(B)

and salts and derivatives thereof as defined under formula (A); wherein X is C_{1-6} alkoxy, NH_2 or hydrogen. The compounds of formula (B) wherein X is C_{1-6} alkoxy or NH_2 are disclosed in EP-A-141927 and the compound of formula (B) wherein X is hydrogen, disclosed in EP-A-182024 (Beecham Group p.l.c.). A particularly preferred example of a compound of formula (B) is that wherein X is hydrogen and wherein the two OH groups are in the form of the acetyl derivative, described in Example 2 of EP-A-182024, hereinafter referred to as famciclovir.

The compounds of formulae (A) and (B) and salts and derivatives thereof have been described as useful in the treatment of infections caused by herpesviruses, such as herpes simplex type 1, herpes simplex type 2 and varicella zoster viruses.

It has now been discovered that these compounds have activity against the hepatitis B virus, and are therefore of potential use in the treatment of hepatitis B virus infections.

Accordingly, the present invention allows for a method of treatment of hepatitis B virus infections in mammals, including humans, which method comprises the administration to the mammal in need of such treatment, an effective amount of a compound of formula (A):



(A)

or a pro-drug, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing.

The term 'acyl derivative' is used herein to include any derivative of the compounds of formula (A) in which one or more acyl groups are present. Such derivatives are included as pro-drugs of the compounds of formula (A) in addition to those derivatives which are per se biologically active.

Examples of pro-drugs, pharmaceutically acceptable salts and derivatives are as described in the aforementioned European Patent references, the subject matter of which are incorporated herein by reference.

A particular pro-drug of interest is 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, known as famciclovir.

The compound of formula (A) may also be in one of the forms disclosed in EP-A-216459 (Beecham Group p.l.c.).

The compound of formula (A), pro-drugs, salts and derivatives may be prepared as described in the aforementioned European patent references.

The compound may be administered by the oral route to humans and may be compounded in the form of syrup, tablets or capsule. When in the form of a tablet, any pharmaceutical carrier suitable for formulating such solid compositions may be used, for example magnesium stearate, starch, lactose, glucose, rice, flour and chalk. The compound may also be in the form of an ingestible capsule, for example of gelatin, to contain the compound, or in the form of a syrup, a solution or a suspension. Suitable liquid pharmaceutical carriers include ethyl alcohol, glycerine, saline and water to which flavouring or colouring agents may be added to form syrups.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

Preferred parenteral formulations include aqueous formulations using sterile water or normal saline, at a pH of around 7.4 or greater.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

An amount effective to treat a hepatitis B virus infection depends on the nature and severity of the infection and the weight of the mammal.

A suitable dosage unit might contain from 50mg to 1g of active ingredient, for example 100 to 500mg. Such doses may be administered 1 to 4 times a day or more usually 2 or 3 times a day. The effective dose of compound will, in general, be in the range of from 0.2 to 40mg per kilogram of body weight per day or, more usually, 10 to 20 mg/kg per day.

The present invention provides the use of a compound of formula (A) or a pro-drug, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing, in the preparation of a medicament for use in the treatment of hepatitis B virus infections in mammals, including humans. Such treatment may be carried out in the manner as hereinbefore described.

The activity of the compounds of formula (A) and pro-drugs, salts, phosphate ester and/or acyl derivatives against hepatitis B virus, may be identified according to the following Test Protocol.

Test for Activity against Hepatitis B virus in ducks

Penciclovir and famciclovir were each tested at two dose levels against hepatitis B virus in ducks. Administration was by oral gavage to two ducks at each dose level.

Dosage was twice daily Monday to Friday inclusive; once daily Saturday and Sunday, continuing for 3 weeks.

The compounds showed activity against duck hepatitis B virus in the above test. Activity was demonstrated by a large reduction in the plasma concentration of duck hepatitis virus DNA and DNA polymerase during treatment. The Table shows the blood levels of administered drug.

TABLE

Blood levels of penciclovir in Pekin ducks after oral dosing with penciclovir or famciclovir

Compound administered	Dose (mg/kg)	Duck No.	Penciclovir concentration (μM) in blood at (min) 15	30	60	120	240	360	AUC[5] (μM hr)
penciclovir[1]	100	142	43	44	40	18	3.6	1.1	92
		163	42	38	44[3]	21	2.7	~0.5	95
	20	139	24	28	18[3]	12	2.8	~0.5	55
		169	41	30	19[3]	10	2.6	N.D.[4]	57
famciclovir[1]	25	111	22	31	34	33	14	6.1	126
		153	18	20[2]	25	20	4.4	~0.5	90
	5	117	8.7	8.4[2]	7.5	2.0	~0.5	N.D.[4]	15
		154	5.1	3.9[2]	3.5	2.0	1.4	1.0	12

Notes

1. Penciclovir administered as a suspension in 1% carboxymethyl cellulose in water containing 1% tween 80. Famciclovir administered as a solution in water.

2. Samples collected at 32 min.

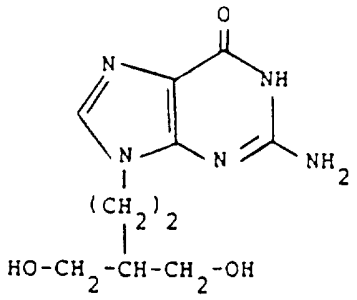
3. Samples collected at 65 min.

4. N.S. = not detected; limit of assay 0.5 μM.

5. AUC = Area under the 0-6 hr. concentration/time curve.

Claims

1. Use of a compound of formula (A):



(A)

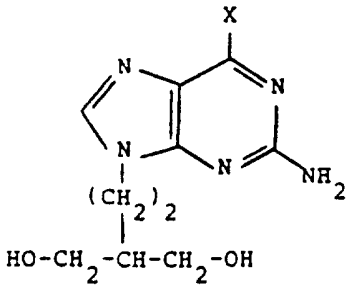
or a pro-drug, or a pharmaceutically acceptable salt, phosphate ester and/or acyl derivative of either of the foregoing; in the manufacture of a medicament for use in the treatment of hepatitis B virus infections.

2. A use according to claim 1 wherein the compound is penciclovir, of formula (A).

3. A use according to claim 1 wherein the compound is the sodium salt hydrate of the compound of formula (A).

4. A use according to claim 3 wherein the medicament is in an aqueous formulation, adapted for parenteral administration.

5. A use according to claim 1 wherein the compound is a pro-drug of the compound of formula (A), of formula (B):



(B)

or a salt or derivative thereof, as defined in respect of formula (A) in claim 1; wherein X is C_{1-6} alkoxy, NH_2 or hydrogen.

6. A use according to claim 5 wherein the pro-drug compound of formula (B) is famciclovir, wherein X is hydrogen and wherein the two OH groups are in the form of the acetyl derivative.

7. A use according to claim 6 wherein the medicament is adapted for oral administration.

8. A use according to claim 1 wherein the compound to be administered is in a 50mg to 1g unit dose.