

PATENT SPECIFICATION

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(54) NUCLEOSIDES AND A PROCESS FOR THE MANUFACTURE THEREOF

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124 - 184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

5 The present invention relates to nucleosides and a process for the manufacture thereof. More particularly, the invention is concerned with pyrimidine nucleosides, which are useful as potent antitumour agents, a process for the manufacture thereof and pharmaceutical preparations containing same. 5

10 The nucleosides provided by the present invention are the compounds 5'-deoxy-5-fluorocytidine and 5'-deoxy-5-fluorouridine and acid addition salts of same. 10

15 The nucleosides provided by the present invention are readily manufactured starting from 5-fluorocytidine or 5-fluorouridine, respectively, by procedures analogous to those which are known for the conversion of cytidine or uridine into the corresponding 5'-deoxy compounds. Thus, for example, a fluoronucleoside starting material can be halogenated in the 5'-position either directly or, more preferably, after ketalisation of the 2'-3'-dihydroxy groups using conventional protecting groups. A resulting 5'-halo compound is then reduced to a 5'-deoxy compound (which, in the case where no ketalisation has been carried out, is the desired end product) either by catalytic hydrogenation or by treatment with a reducing agent such as a complex metal hydride. Where ketalisation has been carried out (i.e. where protecting groups have been used), such groups are removed by hydrolysis in a manner known *per se* so as to yield a desired 5'-deoxy end product. Finally, if desired, 5'-deoxy-5-fluorocytidine and 5'-deoxy-5-fluorouridine may be reacted with a pharmaceutically acceptable acid in a manner known *per se* to yield a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" includes non-toxic salts such as are formed with an inorganic mineral acid or an organic acid such as the hydrochloride, hydrobromide, phosphate, sulphate, nitrate, acetate, formate, maleate, fumarate or benzoate. 25

30 Preferred 2',3'-hydroxy-protecting groups are alkylidene, cycloalkylidene and aralkylidene groups which may be further substituted such as the anisylidene, cyclohexylidene, methoxymethylidene or, most preferably, the isopropylidene or benzylidene group. 30

35 The conversion of 5-fluorocytidine or 5-fluorouridine into a 2',3'-dihydroxy-protected ketal can be carried out according to procedures which are known *per se*. Thus, in one preferred embodiment, a fluoronucleoside is treated with an organic sulphonic acid such as *p*-toluenesulphonic acid and a ketalising agent such as 2,2-dimethoxypropane in a suitable organic solvent such as a ketonic solvent (e.g. acetone). The treatment is carried out at a temperature of from about 0°C to 60°C, most preferably at room temperature. 35

40 Introduction of a halogen atom in the 5'-position can be carried out on either a fluoronucleoside or, more preferably, on a 2',3'-dihydroxy-protected ketal prepared as described earlier. Preferred halogen atoms introduced in accordance with the present invention are iodine and bromine. Thus, for example, an iodine atom can be introduced by 40

reaction with a suitable iodinating agent such as triphenylphosphite methiodide which can be used in the presence of a polar non-protic organic solvent such as dimethylformamide at a temperature of from 0°C to 100°C, most preferably at room temperature. Introduction of a bromine atom can be carried out using a suitable brominating agent such as triphenylphosphine together with carbon tetrabromide. Bromination can be carried out in a dipolar aprotic solvent such as dimethylformamide at a temperature of from 10°C to 100°C.

Conversion of a 5'-halo compound prepared as described earlier into a corresponding 5'-deoxy compound can readily be carried out by catalytic hydrogenation using a noble metal catalyst, which may be supported, such as palladium-on-carbon, palladium-on-barium sulphate, palladium, nickel etc in a protic polar solvent such as an alcohol, preferably methanol. The catalytic hydrogenation is carried out at a temperature of from 0°C to 60°C, preferably at room temperature, and at a pressure of from 1 to 5 atmospheres, most preferably at atmospheric pressure. The catalytic hydrogenation is carried out in the presence of an organic base, preferably a tri (lower alkyl) amine such as triethylamine.

Other suitable reducing agents which can be used to convert a 5'-halo compound into a corresponding 5'-deoxy compound include complex metal hydrides such as tributyl tin hydride, sodium cyanoborohydride or lithium triethylborohydride. This reduction can be carried out at a temperature of from 0°C to 100°C. Suitable solvents for use with the aforementioned reducing agents are well-known.

Removal of the ketal protecting groups, if present, can be readily carried out by hydrolysis using well-known procedures. Thus, for example, the isopropylidene group is cleaved by treatment with trifluoroacetic acid at room temperature.

A further aspect of the present invention relates to the novel intermediates 5'-deoxy-2',3'-O-isopropylidene-5-fluorocytidine and 5'-deoxy-2',3'-O-isopropylidene-5-fluorouridine aforesaid.

The nucleosides provided by this invention (i.e. 5'-deoxy-5-fluorocytidine and 5'-deoxy-5-fluorouridine and pharmaceutically acceptable acid addition salts of same) exhibit activity against Ehrlich carcinoma and sarcoma 180 in mice over a very wide range of dosages both orally and parenterally and are useful as antitumour agents. They can be used as medicaments in the form of pharmaceutical preparations, having direct or delayed release of the active ingredient, which contain them in association with a compatible pharmaceutical carrier material. This carrier material can be an organic or inorganic inert carrier material suitable for enteral, percutaneous or parenteral administration such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkyleneglycols or petroleum jelly. The pharmaceutical preparations can be made up in a solid form (e.g. as tablets, dragées, suppositories or capsules), in a semi-solid form (e.g. as salves) or in a liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain further adjuvants such as preserving, stabilising, wetting or emulsifying agents, flavour-improving agents, salts for variation of the osmotic pressure or substances acting as buffers. The pharmaceutical preparations can be prepared in a conventional manner.

Antitumour testing

The test compounds were dissolved in water for administration to animals.

Sarcoma 180 test

Small pieces of tumour (20-30 mg) were implanted subcutaneously by trocar into the right inguinal region of albino mice weighing 18-20 g. The fragments were obtained from donors bearing firm subcutaneous tumours implanted 7-10 days previously. Treatment was commenced on the day of implantation and was continued once daily for a total of 8 treatments. The mice were killed 8 days after implantation and the tumours were excised and weighed. The ratio of the average weight of the tumours from the untreated control group (C) divided by the average weight of the tumours from the treated group (T) was calculated. The percent inhibition of tumour growth was calculated from the formula:

$$\% \text{ Inhibition} = 100 \frac{(C-T)}{C}$$

The test compound was considered to be active at a particular dose if % inhibition > 50%.

Ehrlich Carcinoma test

The solid form of this tumour was produced by subcutaneous implantation of 0.5 ml of a 1-10 saline-diluted ascitic tumour cell suspension derived from 18-20 g albino donor mice implanted 7-10 days previously. Treatment and evaluation procedures were identical to those used in the aforementioned Sarcoma 180 test.

Results obtained from experiments using the nucleosides provided by the present invention and representative prior art compounds are summarised in Tables 1 and 2 hereinafter.

(12)

TABLE I
Effect of Nucleosides Against Sarcoma 180 Tumour in Mice

5'-Deoxy-5-fluorocytidine					5'-Deoxy-5-fluorouridine				
5	Dose x 8 [mg/kg]		Tested		Inhibition [%]	Tested		Inhibition [%]	5
			Animals	Survivors		Animals	Survivors		
10	400	i.p.	16	14	95				10
	200		16	14	93	16	15	88	
	100		16	16	86	16	16	88	
	50		16	15	72	16	15	89	
15	25	p.o.	16	16	64	16	14	67	15
	12.5		8	8	37	8	7	43	
	400		16	16	92	16	15	90	
	200		16	13	82	16	15	90	
20	100		16	14	76	16	16	83	20
	50		16	16	65	16	16	80	
	25		16	15	76	16	16	75	
	12.5		24	23	62	16	16	73	
25	6.25		8	7	26	15	15	68	25
	3.12					16	16	51	
	1.56					8	8	30	

13

Table 2
Effect of Nucleosides Against Ehrlich Carcinoma in Mice

Compound	Dose x 8 [mg/kg]	Tested Animals	Survivors	Inhibition [%]
5'-Deoxy-5-fluoro- cytidine	400 <i>i.p.</i>	15	14	91
	200	24	23	72
	100	16	16	65
	50	24	23	57
	25	15	15	45
	800 <i>p.o.</i>	8	8	99
	400	16	16	95
	200	24	24	80
	100	24	24	71
	50	16	16	58
	25	16	16	37
5'-Deoxy-5-fluoro- uridine	400 <i>i.p.</i>	16	14	98
	200	24	22	86
	100	24	20	71
	50	24	23	59
	25	24	22	43
	800 <i>p.o.</i>	8	8	99
	400	16	16	98
	200	16	16	90
	100	15	15	70
	50	8	8	56
	25	8	8	27
5'-Deoxyuridine	200 <i>i.p.</i>	8	8	9
	100	8	8	41
2'-5'-Dideoxy-5- -fluorouridine	400 <i>i.p.</i>	16	14	81
	200	16	14	68
	100	16	16	37
	200 <i>p.i.</i>	8	8	34

The following Examples illustrate the process provided by the present invention:

Example 1

A suspension of 92 g of 5-fluorocytidine and 80 g of *p*-toluenesulphonic acid monohydrate in 1500 ml of acetone and 200 ml of 2,2-dimethoxypropane was stirred at room temperature for 2 hours. Excess solid sodium bicarbonate was added and the mixture was stirred until the acid had been completely neutralised. The solids were filtered off and washed with acetone and the filtrate and washings were evaporated to dryness. The residue was triturated with 700 ml of hot ethyl acetate and crystallisation slowly commenced. After storage overnight, the solid was collected, washed with ethyl acetate and dried *in vacuo*. There were obtained 99.5 g (94%) of 2',3'-O-isopropylidene-5-fluorocytidine. A sample was recrystallised from methanol/ethyl acetate and melted at 182°-184°C.

A solution of 32 g of 2',3'-O-isopropylidene-5-fluorocytidine and 60 g of triphenylphosphite methiodide in 300 ml of dry dimethylformamide was stored at room temperature for 1.5 hours. 100 ml of methanol were added and, after 30 minutes, the solution was evaporated to an oil which was partitioned between 700 ml of ethyl acetate and 700 ml of 5% aqueous sodium thiosulphate. The ethyl acetate layer was washed once with 700 ml of aqueous thiosulphate and twice with 700 ml of water and then evaporated to an oil. This oil was dissolved in 400 ml of hot ethyl acetate and hexane was added to the hot solution until crystallisation commenced. After storage at 0°C, the crystals were collected, washed with



hexane and dried *in vacuo*. A second batch of crystals was obtained from the liquors. The total yield was 30.1 g (69%) of 5'-deoxy-5'-iodo-2'-3'-O-isopropylidene-5-fluorocytidine of melting point 192°-194°C.

5 A solution of 48 g of 5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-fluorocytidine in 500 ml of methanol and 20 ml of triethylamine was treated with hydrogen at atmospheric pressure in the presence of 25 g of 5% palladium-on-carbon for 30 minutes at room temperature. During this time, the suspension was agitated using a vibrator. The catalyst was then removed by filtration through Celite (Trade Mark), the filtrate was evaporated to dryness and the residue was triturated with 200 ml of ethyl acetate. After storage overnight, the crystals were removed by filtration, and the filtrate was evaporated to approximately 100 ml and again stored overnight. A second batch of crystals was removed by filtration, the filtrate was evaporated to dryness and the residue was pumped *in vacuo* to give 31 g (93%) of 5'-deoxy-2'-3'-O-isopropylidene-5-fluorocytidine as a foam. This was characterised by formation of a crystalline picrate salt; melting point 168°-170°C.

15 31 g of 5'-deoxy-2'-3'-O-isopropylidene-5-fluorocytidine were treated with 200 ml of 90% trifluoroacetic acid for 40 minutes. The solution was evaporated to dryness, the residue was repeatedly evaporated with portions of ethanol to remove residual water and trifluoroacetic acid and dissolved in 400 ml of ethyl acetate. Triethylamine was added until the solution was alkaline and, after a few minutes, crystallisation commenced. After storage overnight, the crystals were collected, washed with ethyl acetate and dried *in vacuo*. There were obtained 14 g (49%) of 5'-deoxy-5-fluorocytidine. Additional product was obtained by chromatography of the mother liquors on a silica gel column (600 g) which was eluted with 4 litres of ethyl acetate followed by 4 litres of ethyl acetate/methanol (5:1, v/v). The appropriate fractions were evaporated to dryness and applied to a Dowex (Trade Mark) 50 (H⁺) column (2.3 x 60 cm). After a preliminary wash with water, the required material was recovered by elution with 1-N aqueous ammonia. The ammonia fractions were evaporated to dryness and the residue was recrystallised from ethanol. In this way there were obtained as additional 6.7 g of 5'-deoxy-5-fluorocytidine. The total yield was 20.7 g (78%); melting point 209°-211°C (decomposition).

Example 2

1.5 g of 5'-deoxy-5'-iodo-5-fluorocytidine in 30 ml of methanol (30 ml) and 1 ml of triethylamine were treated with hydrogen at atmospheric pressure in the presence of 0.75 g of 10% palladium-on-carbon for 90 minutes at room temperature. During this time the suspension was agitated using a vibrator. The catalyst was removed by filtration and washed with methanol, the combined filtrate and washings were evaporated to dryness and the residue was dissolved in 100 ml of water. The aqueous solution was applied to a Dowex (Trade Mark) 50 (H⁺) column (2.3 x 30 cm) and, after a preliminary wash with 1 litre of water, the required product was obtained by elution with 2 litres of 2-N aqueous ammonium hydroxide. The ammonia eluate was evaporated to dryness, the residue was co-evaporated with two 200 ml portions of ethanol and crystallised from the same solvent to give 0.685 g (69%) of 5'-deoxy-5-fluorocytidine of melting point 207°-208°C.

The starting material was obtained by the following two different methods:

(a) *from 5-fluorocytidine*
45 A solution of 2.61 g of 5-fluorocytidine in 50 ml of dimethylformamide was treated with 5.42 g of triphenylphosphite methiodide for 5 hours at room temperature. Since thin-layer chromatography of the mixture indicated the presence of starting material, a further 5.42 g of triphenylphosphite methiodide were added and the reaction was allowed to proceed for an additional 90 minutes. 10 ml of methanol were added and, after 15 minutes, the solution was evaporated to an oil which was dissolved in 30 ml of ethyl acetate/methanol (1:1, v/v) and applied to a silica gel column (600 g). The column was eluted with ethyl acetate/methanol (10:1, v/v) and 20 ml fractions were collected. Fractions 190-280 were combined, evaporated to a yellow solid and the residue was dissolved in 30 ml of water. The solution was applied to a Dowex (Trade Mark) 50 (H⁺) column (2.3 x 40 cm) and, after a preliminary wash with water, the column was eluted with 2-N ammonium hydroxide. The eluate was evaporated to 200 mg (5.4%) of a crystalline mass. Recrystallisation from ethanol gave pure material of melting point 187°-189°C.

(b) *from 5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-fluorocytidine*
60 A solution of 20 g of 5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-fluorocytidine in 100 ml of trifluoroacetic acid/water (9:1 v/v) was stored at room temperature for 70 minutes. The solution was evaporated to dryness, the residue was co-evaporated with two 200 ml portions of ethanol and dissolved in 200 ml of ethyl acetate. Triethylamine was added until the solution was neutral and, after storage overnight, the crystals were collected and dried. The yield was 16.8 g (93%).

Example 3

- A suspension of 50 g of 5-fluorouridine and 39.3 g of *p*-toluenesulphonic acid monohydrate in 750 ml of acetone and 94 ml of 2,2-dimethoxypropane was stirred at room temperature for 50 minutes. Excess solid sodium bicarbonate was added to clear solution and the mixture was stirred until neutral. The solids were removed by filtration and washed with acetone, and the filtrate and washings were combined and evaporated to dryness. The residual solid was recrystallised from 2 litres of ethyl acetate to give 48 g (83%) of 2',3'-O-isopropylidene-5-fluorouridine of melting point 196°-197°C.
- A solution of 46.4 g of 2',3'-O-isopropylidene-5-fluorouridine in 250 ml of dry dimethylformamide was treated with 86.7 g of triphenylphosphite methiodide and stored at room temperature for 50 minutes. 250 ml of methanol were added and, after 30 minutes, the solution was evaporated to an oil which was partitioned between 1 litre of ethyl acetate and 1 litre of 5% aqueous sodium thiosulphate. The ethyl acetate layer was washed with two 1 litre portions of water, dried overnight over sodium sulphate and evaporated to dryness. The oil was crystallised from 350 ml of ethyl acetate. There were obtained 52.9 g (85%) of 5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-fluorouridine of melting point 202°-203°C.
- A solution of 24 g of 5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-fluorouridine in 800 ml of methanol and 15 ml of triethylamine was treated with hydrogen at atmospheric pressure in the presence of 12 g of 5% palladium-on-carbon for 90 minutes at room temperature. The mixture was agitated during this time using a vibrator. The catalyst was removed by filtration through Celite (Trade Mark) and washed with methanol. The combined filtrate and washings were evaporated to dryness, the residue was triturated with 200 ml of ethyl acetate for 1 hour and the crystals were removed by filtration. The filtrate was evaporated to approximately half volume, stored overnight and filtered again to remove a second batch of crystals. The filtrate was evaporated to dryness, the residue was pumped *in vacuo* and the resulting 5'-deoxy-2',3'-O-isopropylidene-5-fluorouridine [UV (methanol): λ_{max} 204 nm ($\epsilon = 10900$) and 267 nm ($\epsilon = 8670$); IR (potassium bromide): 3380, 3200, 1710, 1670 cm^{-1}] was treated with 200 ml of 90% aqueous trifluoroacetic acid for 1 hour. The product was evaporated to dryness, repeatedly co-evaporated with ethanol to remove water and trifluoroacetic acid and recrystallised from ethyl acetate to give 1.35 g (79%) of 5'-deoxy-5-fluorouridine of melting point 189°-190°C.

Example 4

- A solution of 291 mg of 5'-deoxy-5'-iodo-5-fluorouridine in 10 ml of methanol and 0.5 ml of triethylamine was hydrogenated at atmospheric pressure in the presence of 145 mg of 5% palladium-on-carbon. After 1.5 hours, the catalyst was removed by filtration, the filtrate was evaporated to dryness and the residue was dissolved in a minimum amount of hot ethyl acetate. On cooling, crystals of triethylammonium iodide were deposited. These crystals were removed by filtration, the filtrate was evaporated to dryness and the residue was recrystallised from ethanol. There were obtained 130 mg (68%) of 5'-deoxy-5-fluorouridine.
- The starting material was obtained by the following two different procedures:
- (a) *from 5-fluorouridine*
- A solution of 2.62 g of 5-fluorouridine in 50 ml of dimethylformamide was treated with 5.42 g of triphenylphosphite methiodide for 1.75 hours at room temperature. 10 ml of methanol were added and, after 30 minutes, the solution was evaporated to an oil which was dissolved in 30 ml of ethyl acetate and applied to a silica gel column (500 g). The column was eluted with ethyl acetate and 20 ml fractions were collected. Fractions 61-130 were combined and evaporated to dryness, and the residue was dissolved in 50 ml of hot ethyl acetate. Addition of 10 ml of hexane gave crystalline material. After storage at room temperature overnight, the crystals were collected, washed with hexane and dried *in vacuo*. A second crop was obtained from the mother liquors. The total yield was 1.13 g (30%); melting point 174.5°-175.5°C.
- (b) *from 5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-fluorouridine*
- 4 g of 5'-deoxy-5'-iodo-2',3'-O-isopropylidene-5-fluorouridine were treated with 30 ml of trifluoroacetic acid/water (9:1, v/v) for 15 minutes at room temperature. The solution was evaporated to dryness, co-evaporated with two 100 ml portions of ethanol and the residue was recrystallised from ethyl acetate. The yield was 1.865 g (88%).
- The following Examples illustrate pharmaceutical preparations containing the nucleosides provided by the present invention:

*Example A**Wet granulation tablet formulations:*

		mg/tablet	mg/tablet	
5	1. 5'-Deoxy-5-fluorouridine or 5'-deoxy-5-fluorocytidine	250	500	5
	2. Pregelatinised starch	25	50	
	3. Modified starch	25	50	
10	4. Corn starch	25	50	10
	5. Stearic acid	2.5	2.5	
	6. Magnesium stearate	1.5	3.0	
		<u>329.0</u>	<u>655.5</u>	

15 Items 1, 2, 3, and 4 are mixed. The mixture is granulated with water, dried overnight and milled. Items 5 and 6 are added in the form of a premix. The resulting mixture is mixed for 5 minutes and then compressed to tablets at a suitable pressure.

Example B

		mg/tablet	mg/tablet	
20	1. 5'-Deoxy-5-fluorouridine or 5'-deoxy-5-fluorocytidine	250	500	20
	2. Polyvinylpyrrolidone	25	50	
25	3. Modified starch	25	50	25
	4. Corn starch	25	50	
	5. Magnesium stearate	2.5	5.0	
		<u>327.5</u>	<u>655.0</u>	

30 Items 1, 3 and 4 are mixed in a suitable mixer. The mixture is granulated with item 2 in alcohol. The mixture obtained is dried overnight and milled. Item 5 is added and the resulting mixture is compressed to tablets on a suitable press.

Example C

		mg/capsule	mg/capsule	
35	<i>Capsule formulations:</i>			35
	1. 5'-Deoxy-5-fluorouridine or 5'-deoxy-5-fluorocytidine	250	500	
40	2. Corn starch	50	50	40
	3. Magnesium stearate	2	5	
	4. Talc	10	20	
		<u>312</u>	<u>575</u>	

45 Items 1 and 2 are mixed in a suitable mixer for 10 minutes. Items 3 and 4 are added and the mixture obtained is mixed for 5 minutes. The resulting mixture is filled into capsules on a suitable machine.

Example D

50	<i>Dry parenteral dosage forms:</i>			50
	(1) 5 g of 5'-deoxy-5-fluorocytidine or 5'-deoxy-5-fluorouridine are dissolved in 75 ml of distilled water, the solution is subjected to a bacteriological filtration and then divided aseptically into 10 sterile vials. The solution is then freeze dried to yield 500 mg of sterile dry solid per vial.			
55	(2) Clean lint-free crystals of 5'-deoxy-5-fluorocytidine or 5'-deoxy-5-fluorouridine (500 mg per vial or ampule) are sealed in the receptacle which is then heat sterilised.			55
	The aforementioned dry dosage forms are reconstituted before use by adding a suitable sterile aqueous solvent such as water for injection or isotonic sodium chloride or 5% dextrose for parenteral administration.			
60	WHAT WE CLAIM IS:-			60
	1. 5'-deoxy-5-Fluorocytidine and 5'-deoxy-5-fluorouridine and pharmaceutically acceptable acid addition salts of same.			
65	2. 5'-deoxy-5-fluorocytidine.			65
	3. 5'-deoxy-5-fluorouridine.			

**Example A****Wet granulation tablet formulations:**

		mg/tablet	mg/tablet	
5	1. 5'-Deoxy-5-fluorouridine or 5'-deoxy-5-fluorocytidine	250	500	5
	2. Pregelatinised starch	25	50	
	3. Modified starch	25	50	
10	4. Corn starch	25	50	10
	5. Stearic acid	2.5	2.5	
	6. Magnesium stearate	1.5	3.0	
		<u>329.0</u>	<u>655.5</u>	

15 Items 1, 2, 3, and 4 are mixed. The mixture is granulated with water, dried overnight and milled. Items 5 and 6 are added in the form of a premix. The resulting mixture is mixed for 5 minutes and then compressed to tablets at a suitable pressure. 15

Example B**Wet granulation tablet formulations:**

		mg/tablet	mg/tablet	
20	1. 5'-Deoxy-5-fluorouridine or 5'-deoxy-5-fluorocytidine	250	500	20
	2. Polyvinylpyrrolidone	25	50	
25	3. Modified starch	25	50	25
	4. Corn starch	25	50	
	5. Magnesium stearate	2.5	5.0	
30		<u>327.5</u>	<u>655.0</u>	30

Items 1, 3 and 4 are mixed in a suitable mixer. The mixture is granulated with item 2 in alcohol. The mixture obtained is dried overnight and milled. Item 5 is added and the resulting mixture is compressed to tablets on a suitable press.

Example C**Capsule formulations:**

		mg/capsule	mg/capsule	
35	1. 5'-Deoxy-5-fluorouridine or 5'-deoxy-5-fluorocytidine	250	500	35
	2. Corn starch	50	50	
40	3. Magnesium stearate	2	5	40
	4. Talc	10	20	
45		<u>312</u>	<u>575</u>	45

Items 1 and 2 are mixed in a suitable mixer for 10 minutes. Items 3 and 4 are added and the mixture obtained is mixed for 5 minutes. The resulting mixture is filled into capsules on a suitable machine.

Example D**Dry parenteral dosage forms:**

(1) 5 g of 5'-deoxy-5-fluorocytidine or 5'-deoxy-5-fluorouridine are dissolved in 75 ml of distilled water, the solution is subjected to a bacteriological filtration and then divided aseptically into 10 sterile vials. The solution is then freeze dried to yield 500 mg of sterile dry solid per vial.

(2) Clean lint-free crystals of 5'-deoxy-5-fluorocytidine or 5'-deoxy-5-fluorouridine (500 mg per vial or ampule) are sealed in the receptacle which is then heat sterilised.

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

WHAT WE CLAIM IS:-

1. 5'-deoxy-5-Fluorocytidine and 5'-deoxy-5-fluorouridine and pharmaceutically acceptable acid addition salts of same.

2. 5'-deoxy-5-fluorocytidine.

3. 5'-deoxy-5-fluorouridine.

4. A process for the manufacture of 5'-deoxy-5-fluorocytidine and 5'-deoxy-5-fluorouridine and pharmaceutically acceptable acid addition salts of same, which process comprises

(a) removing the 2',3'-O-protecting group of a 2',3'-ketalised 5'-deoxy-5-fluorocytidine or 2',3'-ketalised 5'-deoxy-5-fluorouridine by hydrolysis, or

(b) reducing a 5'-deoxy-5'-halo-5-fluorocytidine or 5'-deoxy-5'-halo-5-fluorouridine in 5'-position, and, if desired, reacting the resulting 5'-deoxy-5-fluorocytidine or 5'-deoxy-5-fluorouridine with a pharmaceutically acceptable acid.

5. A process as claimed in claim 4, wherein the 2',3'-O-protecting group is an alkylidene, cycloalkylidene or aralkylidene group which may be substituted.

6. A process as claimed in claim 5, wherein the 2',3'-O-protecting group is the isopropylidene group.

7. A process as claimed in claim 6, wherein 5'-deoxy-2',3'-O-isopropylidene-5-fluorocytidine or 5'-deoxy-2',3'-O-isopropylidene-5-fluorouridine is hydrolysed with trifluoroacetic acid.

8. A process as claimed in claim 4, wherein the reduction is carried out by catalytic hydrogenation.

9. A process as claimed in claim 4, wherein the reduction is carried out using a complex metal hydride.

10. A process as claimed in claim 4, claim 8 or claim 9, wherein 5'-deoxy-5'-iodo-5-fluorocytidine or 5'-deoxy-5'-iodo-5-fluorouridine is reduced.

11. A process for the manufacture of the nucleosides set forth in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 4.

12. A nucleoside as set forth in claim 1, when manufactured by the process claimed in any one of claims 4 to 11 inclusive or by an obvious chemical equivalent thereof.

13. A pharmaceutical preparation containing a nucleoside as set forth in claim 1 in association with a compatible pharmaceutical carrier material.

14. 5'-Deoxy-2',3'-O-isopropylidene-5-fluorocytidine.

15. 5'-Deoxy-2',3'-O-isopropylidene-5-fluorouridine.

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