

PATENT SPECIFICATION

(11) 1353 565

1353 565

- (21) Application No. 22419/72 (22) Filed 12 May 1972
 (31) Convention Application No. 149017 (32) Filed 1 June 1971
 (31) Convention Application No. 240252 (32) Filed 31 March 1972 in
 (33) United States of America (US)
 (44) Complete Specification published 22 May 1974
 (51) International Classification C07D 99/04 A61K 21/00 C07F 9/08
 (52) Index at acceptance

C2C 1450 1472 215 220 226 22Y 247 250 252 253 25Y
 28X 29X 29Y 302 30Y 320 326 342 34Y 360
 361 362 364 366 368 36X 36Y 37X 380 43X
 509 50Y 574 628 62X 633 638 643 644 648
 652 658 65X 668 676 678 67X 699 723 746
 752 75X 76X 780 790 BG KK KP LA MC
 SN

C2A 1C2A 1C2C 2A3 3A1

C2P 2E13 2E15A 2E16 2E19B 2E19D 2E26A 2E26C
 2E26E 5B 6 7

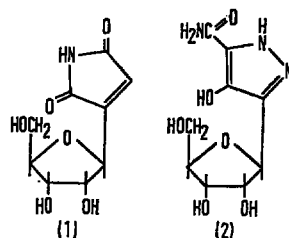


(54) 1,2,4-TRIAZOLE NUCLEOSIDES

(71) We, I.C.N. PHARMACEUTICALS INC., previously known as International Chemical & Nuclear Corporation, a Corporation organised and existing under the Laws of the State of California, United States of America, of 171 South Lake Avenue, Pasadena, State of California 91101, United States of America, 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:—

This invention relates to 1,2,4, triazole nucleosides.

Up to the present time the only two known nucleosidic antibiotic agents having 5-membered heterocyclic rings were showdomycin and pyrazomycin, which have respectively been reported to have structures 1 and 2:

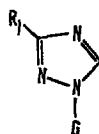


Among the known synthetic nucleosidic antiviral agents, the more important are 5-iodo-2'-deoxyridine (5-IDU) 9-β-D-arabinofuranosyl adenine (Ara-A) and 1-β-D-arabinofuranosyl cytosine (Ara-C). Of these agents, only 5-IDU [in 0.1% wt. solution] is commercially available specifically as an antiviral agent, and this compound suffers the disadvantage of low solubility and high toxicity (hence the undesirably great dilution in which it is now employed).

Alonso, et al in *J. Heterocyclic Chem.* 7, 1269—72 (1970) report the preparation of 1-(β-D-ribofuranosyl)-4-carboxamido-1,2,3-triazole but make no mention of biological activity. Witowski and Robins, in "The Chemical Synthesis of the 1,2,4-Triazole Nucleosides related to Uridine, 2'-Deoxyuridine, Thymidine and Cytidine", *J. Org. Chem.* 35, 2635—41 (1970) suggest various 1,2,4-triazole nucleoside analogs as candidates for biological testing, but no particular efficacy is noted and our later testing has shown that, of the analogs there reported, only 5-bromo-3-nitro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,4-triazole exhibits even slight antiviral activity and even this activity is believed to be attributable merely to cytotoxicity of the compound.

Accordingly the present invention provides compounds of the formula

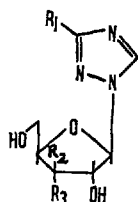
[Price 25p]



wherein "G" is a furanosyl moiety, preferably characterized by having its 2' oxygen *trans* to the triazole aglycon, R₁ being cyano-, carboxamido-, thiocarboxamido-, methyl-carboxylate, carboxamidoxime, -carboxamidine, or a physiologically acceptable acid addition salt of the latter group. The invention also embraces the *O*-acylated analogs of the foregoing compounds and the 5'-phosphates and 3',5'-cyclic phosphates thereof as well as the ammonium and alkali metal salts of the phosphates.

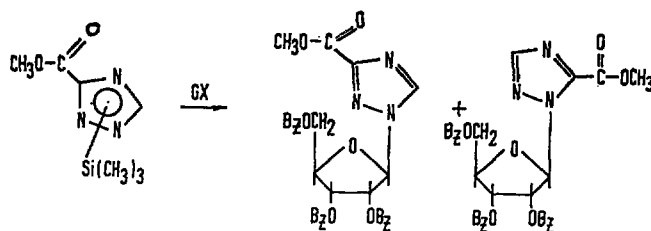
The furanosyl moiety, "G", may be, for example, a xylofuranosyl, ribofuranosyl, 2'-*O*-methylribofuranosyl or arabinofuranosyl group.

A preferred embodiment of the invention is a compound having the structure



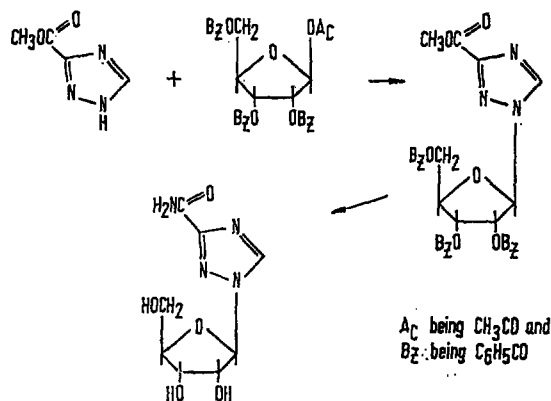
where R₁ is as hereinbefore defined and one of R₂ or R₃ is hydrogen, the other being hydroxyl, as well as 5'-phosphates and 3',5'-cyclic phosphates thereof. The compounds of the present invention exhibit antiviral activity, and, in non-acylated or "deblocked" embodiments, exhibit substantially greater aqueous solubility than earlier reported nucleosidic antiviral agents. The preferred 1-(β-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide nucleoside of the invention has exhibited a broad spectrum of antiviral activity as well as antitumor activity.

Methyl 1,2,4-triazole-3-carboxylate and 3-cyano-1,2,4-triazole are precursors in alternative synthetic routes leading to the 1,2,4-triazole nucleosides of the present invention. The former compound can be conventionally prepared by oxidation of 3-methyl-1,2,4-triazole followed by esterification of the resulting acid according to the procedure of Cipens and Grinsteins' *Latvijas PSR Zinatnu Akad. Vestis.*, Kim. Ser. (1965) (2) 204—08 (See *C.A.* 63, 13243, 1965). 3-Cyano-1,2,4-triazole is prepared by a multi-step synthesis reported by Cipens et al, *supra*, or more conveniently, by the addition reaction of cyanogen and hydrazine to form 1-cyanoformimidic acid hydrazide, followed by acid-catalysed ring closure in triethylorthoformate to the 3-cyano compound. By one route, the trimethylsilyl derivative of the methyl 1,2,4-triazole-3-carboxylate is formed in quantitative yield by reaction with hexamethyldisilazane under reflux and reacted with an appropriate *O*-acylated halo sugar to form, for example, a mixture of *O*-benzoylated 1-(β-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester and 5-carboxylic acid methyl ester, i.e.:



wherein Bz is benzoyl. The 3-carboxylic acid methyl ester is separated by fractional crystallization or, preferably, by column chromatography over silica gel. Debenzoylation and aminolysis gives, in this case, the 1-(β-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide.

The preferred method of synthesis is by the acid-catalyzed fusion of an appropriately substituted triazole with the *O*-acyl blocked sugar (in this case 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -*D*-ribofuranose) followed by deacylation and aminolysis, i.e.:

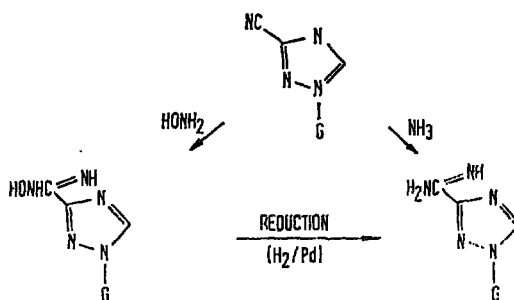


Alternatively fusion may be achieved with 3-cyano-1,2,4-triazole with subsequent conversion of the resulting 3-cyano-1-(2,3,5-tri-*O*-acetyl- β -*D*-ribofuranosyl)-1,2,4-triazole to the active 3-carboxamido nucleoside by reaction with hydrogen peroxide in the presence of aqueous ammonia. Yields are, however, less than when fusion occurs with methyl 1,2,4-triazole-3-carboxylate.

It will be understood that the "silylation" and "fusion" processes described above with specific reference to the preparation of β -*D*-ribofuranosyl derivatives, may be employed for the preparation of nucleosides of the invention in which the group "G" is other than β -*O*-ribofuranosyl.

3-cyano-1-(2,3,5-tri-*O*-acetyl- β -*D*-ribofuranosyl)-1,2,4-triazole, whether obtained by the "silylation" or "fusion" process, is a useful starting material in the formation of the active 1-(β -*D*-ribofuranosyl)-1,2,4-triazole-3-thiocarboxamide nucleosides of the present invention, by reaction with hydrogen sulfide in the presence of triethylamine followed by the deacylation where the blocked nucleoside is employed as the starting material. Similarly, 1-furanosyl-1,2,4-triazole-3-thiocarboxamide may be prepared from 3-cyano-1-(*O*-acylated furanosyl)-1,2,4-triazole as the starting material or from 3-cyano-1-furanosyl-1,2,4-triazole as the starting material.

Similarly, the nucleosidic 1,2,4-triazole-3-carboxamides can be made from the 3-cyano-1,2,4-triazole nucleoside either with or without intermediate formation of the 3-carboxamidoxime analog, i.e.:



where G is a glycosyl moiety as hereinbefore defined. The carboxamide is obtained in free form from the synthesis involving the carboxamidoxime intermediate. The preferred preparation directly from the 3-cyano compound in the presence of ammonium chloride yields, however, the carboxamide in the form of its hydrochloride salt. Other physiologically acceptable acid addition salts (e.g., hydrobromic, hydroiodic, citric, acetic, sulfuric, phosphoric acid addition salts) may be obtained therefrom by ion exchange, or, alternatively, by neutralization of the hydrogen chloride salt with sodium bicarbonate followed by reaction of the resulting free carboxamide with an appropriate acid. For example, when the group "G" is β -*D*-ribofuranosyl the compound 1-(β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide may be prepared.

The 3-carboxamido, 3-thiocarboxamido and 3-carboxamide nucleosides of the

present invention may each be converted to the corresponding 5'-phosphate or to the ammonium or alkali metal salt of the phosphate and administered as such. Similarly, 5'-phosphates of the intermediate 3-methyl carboxylates, 3-cyano- and 3-carboxamidoxime compounds of the invention may be formed prior to operations involving position 3 of the triazole aglycon and leading to the formation of the active nucleotides. The method and manner of phosphorylating nucleosides will be familiar to those skilled in the art. In a preferred embodiment of the present invention, the 5'-phosphate of 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide is formed by reaction of 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester with POCl₃ in trimethyl phosphate, followed by hydrolysis in ice water to yield the free 5'-phosphate. Formation of the ammonium salt and aminolysis of the methyl ester occur simultaneously on treatment with aqueous ammonia. Corresponding alkali metal salts or the free 5'-phosphate of the 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide nucleotide can then be obtained from the ammonium salt thereof by ion exchange.

It will be understood that the process for the preparation of 5'-phosphate derivatives, or corresponding ammonium or alkali metal salts thereof, which has been described above with specific reference to 1-(β -D-ribofuranosyl) derivatives may be used in the production of nucleotides in which the "G" group is other than 1-ribofuranosyl.

The 3',5'-cyclic phosphates of the active carboxamido, thiocarboxamido and carboxamidine compounds of the present invention may be secured by dicyclohexylcarbodiimide (DCC) cyclization of corresponding 5'-phosphates. Alternatively, 5'-phosphates of the cyano-, methylcarboxylate and carboxamidoxime intermediates may be cyclized prior to operations involving position 3 of the aglycon and leading to said active cyclic nucleotides. In either case, the cyclic phosphates may be employed either in the free form or in the form of the ammonium or alkali metal salts obtained as in the case of the 5'-phosphates. The ammonium salt may, alternatively, be converted to the free form by ion exchange. The 3',5'-cyclic phosphate compounds of the present invention exhibit enhanced cellular transport compared to the 5'-phosphate. This process for the preparation of 3',5'-phosphate derivatives may, of course, be used in the production of nucleosides in which the glycidyl group is other than 1-ribofuranosyl.

While the invention has been described with particular reference to acetyl or benzoyl blocking of the 2', 3' and 5' hydroxyls of the glycosyl moiety, it will be understood that any acyl group may be employed to protect these hydroxyl groups against side reactions (such as dehydration) during synthesis of the active agents of the present invention. Sutherland, et al, in *Biochim. et Biophys Acta* 148, 106 (1967) have reported that the acylation of cyclic nucleotides enhances cellular transport. Similarly, otherwise free glycosyl hydroxyl groups of the nucleotides and nucleosides of the present invention may be acylated to thereby result in enhanced lipid solubility or may be provided with alkyl or alkaryl sulfonyl groups such as tosyl, mesyl, bromobenzene sulfonyl and nitrobenzene sulfonyl groups to the same end.

While the 1'-"leaving group" of the sugar reagents discussed above has been illustrated by the acetyl group or, in the case of the silylation procedure, a halogen atom, it will be understood that any displacable moiety may be employed subject to amenability to byproduct separation.

In addition, by way of illustration of the aforementioned processes, reference has been to β -D-ribofuranosyl and xylfuranosyl moieties. It will, however, be appreciated that other glycosyl moieties may be employed as well, e.g. 2'-deoxy- β -D-ribofuranosyl, 2'-deoxy- α -D-ribofuranosyl, 2'-O-methylribofuranosyl and β -D-arabinofuranosyl. In the case of the 2'-deoxy triazole nucleosides, precursor sugars employed may include 2-deoxy-1,3,5-tri-O-acetyl-D-ribofuranose or 1-O-acetyl-2-deoxy-3,5-di-O-(para-toluoyl)-D-ribofuranose; the latter results from treatment of 2-deoxy-3,5-di-O-(para-toluoyl)-D-ribofuranosyl chloride with mercuric acetate in tetrahydrofuran.

The arabinosyl triazole nucleosides are made by the silylation procedure, employing 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride.

Given the biological activity of the ribofuranosyl triazoles of the present invention, biological activity associated with the correspondingly substituted arabinofuranosyl triazoles would be predicted, especially in view of the known antiviral activity of "Ara-A" and "Ara-C" as discussed above. Similarly, given efficacy of the ribofuranosyl triazoles of the present invention, especially against essentially DNA viruses such as Herpes Types 1 and 2, biological activity associated with the corresponding 2'-deoxy- β -D-ribofuranosyl triazoles is suggested by the known antiviral activity of 5-iodo-2'-deoxy uridine. However, when these compounds were tested against the viruses of Example 16, *infra*, essentially no antiviral activity was seen, apparently, as a result of the inability of the enzymes present in the tissue culture to phosphorylate free nucleosides whose glycosyl moieties lack *trans* 2'-oxygen atoms. Hence, these nucleosides

should be synthetically phosphorylated to the believed active 5'-phosphate form prior to administration. Alternatively, the 5'-phosphate may be cyclised before administration, *in vivo* cleavage yielding the active 5'-phosphate. The phosphorylation procedure is essentially the same as that described above for the preparation of the ribotides.

The invention will now be further illustrated and described in the following specific Examples, in which all parts and percentages are by weight and all temperatures in degrees Centigrade unless otherwise stated. All evaporative procedures were carried out in a rotary evaporator under diminished pressure at 35°C.

EXAMPLE 1

1-(2,3,5-Tri-*O*-benzoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester and 1-(2,3,5-Tri-*O*-benzoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-5-carboxylic Acid Methyl Ester, (Silylation Procedure).

(A) Preparation of Methyl N-(Trimethylsilyl)-1,2,4-triazole-3-carboxylate

A suspension of methyl 1,2,4-triazole-3-carboxylate (14.0 g, 110 mmole) and hexamethyldisilazane (100 ml) was refluxed with stirring until evolution of ammonia ceased (*ca.* 2 hrs.). The excess hexamethyldisilazane was removed under diminished pressure to provide 20.6 g (100%) of the N-trimethylsilyl derivative of methyl 1,2,4-triazole-3-carboxylate.

(B) Ribosylation with Halo Sugar

A solution containing methyl N-(trimethylsilyl)-1,2,4-triazole-3-carboxylate (20.6 g, 110 mmole) and 2,3,5-tri-*O*-benzoyl-*D*-ribofuranosylbromide (52.5 g, 100 mmole) in anhydrous acetonitrile (300 ml) was kept at 25° for 3 days. The solvent was removed and the residue was crystallized from ethanol. Recrystallization of the material from ethyl acetate-ethanol and column chromatography of the filtrates over silica gel with chloroform provided pure 1-(2,3,5-tri-*O*-benzoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (25.1 g, 44.0%) with mp 137—139°.

Anal. Calcd for $C_{30}H_{25}N_3O$: C, 63.04; H, 4.41; N, 7.35

Found: C, 62.91; H, 4.17; N, 7.10

The faster migrating component from the silica gel column was crystallized from ethanol to provide 1-(2,3,5-tri-*O*-benzoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (13.2 g, 23.1%) with mp 122—124°.

Anal. Found: C, 63.20; H, 4.35; N, 7.12.

EXAMPLE 2

1-(2,3,5-Tri-*O*-benzoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester. (Fusion Procedure)

A mixture of methyl 1,2,4-triazole-3-carboxylate (12.7 g, 100 mmole) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -*D*-ribofuranose (55.4 g, 110 mmole) was heated in an oil bath maintained at 160—165°. After the sugar had melted, bis(*p*-nitrophenyl)phosphate (400 mg) was added with stirring and the mixture was heated under diminished pressure at 160—165° for 15—20 min. Crystallization of the residue from ethyl acetate-ethanol provided 42.5 g (74.5%) of product with mp 137—139°.

EXAMPLE 3

1-(2,3,5-Tri-*O*-acetyl- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester

A mixture of methyl 1,2,4-triazole-3-carboxylate (12.7 g, 0.10 mol) and 1,2,3,5-tetra-*O*-acetyl- β -*D*-ribofuranose (31.8 g, 0.10 mol) was heated in an oil bath maintained at 160—165° until the sugar had melted. Bis(*p*-nitrophenyl) phosphate (250 mg) was added and heating at 160—165° was continued with stirring under diminished pressure for 15—20 min. The residue was dissolved in hot benzene, the solution was filtered and cyclohexane was added to the filtrate to give the crystalline product (30.0 g, 77.8%) with mp 107—109°.

Anal. Calcd for $C_{15}H_{19}N_3O_9$: C, 46.75; H, 4.97; N, 10.91

Found: C, 46.88; H, 5.03; N, 10.64

EXAMPLE 4

1-(β -*D*-Ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester
A solution of 1-(2,3,5-tri-*O*-benzoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic

acid methyl ester (25.0 g., 43.8 mmol) and sodium methoxide (400 mg) in methanol (200 ml) was refluxed for 45 min. The solution was neutralized with Bio-Rad AG50-X2(H), filtered and the filtrate was concentrated to a syrup. Crystallization of the syrup from methanol-ethyl acetate provided 8.0 g (70.5%) of product with mp 117—119°.

Anal. Calcd for $C_9H_{13}N_3O_6$: C, 41.70; H, 5.06; N, 16.21
Found: C, 41.57; H, 5.13; N, 16.16

EXAMPLE 5

(A) 1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide

Method 1:

A solution of 1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (16.0 g, 28.0 mmole) in methanol (300 ml, presaturated with anhydrous ammonia at 0°) was kept in a sealed pressure flask at 25° for 3 days. The solvent was removed and the product was crystallized from ethanol to give 6.7 g (98%) of material with mp 174—176°. Recrystallization of the product from aqueous ethanol provided a second crystalline form of the nucleoside with mp 166—168°.

Anal. Calcd for $C_8H_{12}N_4O_5$: C, 39.34; H, 4.95; N, 22.94
Found: C, 39.08; H, 5.10; N, 22.67

(B) 1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide

Method 2:

A solution of 1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (10.0 g, 26.0 mmole) in methanol (70 ml) saturated at 0° with anhydrous ammonia was kept in a sealed pressure flask at 25° for 18 hrs. The product was crystallized from ethanol to give 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (5.70 g, 90.0%).

(C) 1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide

Method 3:

A mixture of 3-cyano-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole (705 mg, 2.0 mmole), 28% aqueous ammonia (20 ml) and 30% hydrogen peroxide (3.0 ml) was stirred at 25° for 6 hours. An additional 3.0 ml portion of 30% hydrogen peroxide was then added and stirring at 25° was continued for 12 hrs. The excess hydrogen peroxide was destroyed by addition of platinum black, the solution was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in methanol and silica gel (5.0 g) was added to the solution. The solvent was removed and the silica gel mixture was applied to a silica gel column. Elution with ethyl acetate-methanol (1:1) provided 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (250 mg, 51.2%).

EXAMPLE 6

1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide 3',5'-cyclic phosphate ammonium salt

To 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide 5'-phosphate ammonium salt (5.7 g, 15.9 mmole) in pyridine was added 4-morpholine-N,N'-dicyclohexylcarboxamidine (4.65 g, 15.9 mmole) and the resulting solution was evaporated *in vacuo* several times with pyridine to an anhydrous syrup. The syrup was dissolved in 1 liter of pyridine and added dropwise (over a one hour period), through a reflux condenser, into a refluxing anhydrous solution of dicyclohexylcarbodiimide (16.4 g, 79.6 mmole) in 3 liters of pyridine. The solution was refluxed for a further two hours and 200 ml water was added slowly. After *ca.* 12 hours the solution was evaporated *in vacuo* and to the residue was added 200 ml water and 50 ml ether. The suspension was stirred vigorously and then filtered. The aqueous layer was separated and extracted with 2×100 ml ether. The aqueous layer was passed through Dowex 50 (NH_4^+ form, 100—200 mesh) and the eluant evaporated to a syrup. Ethanol *ca.* 100 ml was added to the syrup and the resulting mixture stood at room temperature *ca.* 12 hours. The crude precipitate

(D) 1-(2-Deoxy- α -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide

A solution of 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl- α -D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (780 mg, 1.63 mmol) in methanol (25 ml) saturated at 0° with anhydrous ammonia was kept in a sealed pressure flask at 25° for 3 days. The solvent was removed and the crude product was applied to a silica gel column. Elution with ethyl acetate-methanol (9:1) provided 1-(2-deoxy- α -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (350 mg, 94.4%) as an amorphous solid.

Anal. Calcd for $C_8H_{12}N_4O_4$: C, 42.10; H, 5.30; N, 24.55
Found: C, 41.88; H, 5.48; N, 24.29

By using the same procedure as was employed to convert the separated methyl ester anomers to their respective carboxamides, the anomeric mixture of the methyl esters formed in part (B) above may be reacted with ammonia to yield a mixture of the α and β anomers of the carboxamide.

EXAMPLE 16

Antiviral agents of the present invention were tested for activity against both small and large viruses of both DNA and RNA types by the virus rating (VR) method of Sidwell, et al., *Appl. Microbiol.* 22, 797 (1971). V.R. > 1.0 is indicative of definite antiviral activity, V.R. of 0.5—0.9 is indicative of moderate antiviral activity, and V.R. < 0.5 suggests slight or no apparent antiviral activity. The results reported below, which for comparison sake include data taken with various known antiviral agents, were obtained by testing on Microtest II (Falcon Plastics) plastic panels with a monolayer of KB or RK13 cells.

Of the viruses employed in the test, herpes type 1 is implicated in labialis (cold sores), herpes keratitis and herpes encephalitis. Herpes type 2 causes herpes genitalis, a common and communicable form of venereal disease. Myxoma causes death in domestic and wild rabbits and is preceded by respiratory illness and severe swelling. Pseudorabies causes infectious bulbar paralysis, also known as the "mad itch" disease in cattle, sheep, pigs, dogs and mink. Parainfluenza virus causes a mild upper respiratory illness in humans, especially small children, and is implicated in cattle conjunctivitis. Vaccinia is an avirulent form of smallpox virus employed for smallpox vaccination, and its use occasionally results in undesired side effects. Rhino type 13 is one of the many viruses involved in the common cold.

methylene chloride-cyclohexane to provide 1.3 g (12.6%) of 1-(2,3,5-tri-*O*-benzyl- β -*D*-arabinofuranosyl)-1,2,4-triazole-3-carboxamide with mp 100—102°.

Anal. Calcd for $C_{23}H_{30}N_4O_5$: C, 67.69; H, 5.88; N, 10.89
Found: C, 67.82; H, 5.70; N, 10.94

5 A suspension of palladium black and methanol (20 ml) was prepared by reduction of palladium chloride (300 mg) with hydrogen and to this was added a solution of 1-(2,3,5-tri-*O*-benzyl- β -*D*-arabinofuranosyl)-1,2,4-triazole-3-carboxamide (600 mg) in methanol (25 ml). The mixture was shaken on a hydrogenation apparatus at 25 psi for 2 hrs at 20°. The catalyst was removed by filtration and the solution was passed through a column of Amberlite IR45(OH) (15 ml). The solvent was removed and the residue was crystallized from ethanol to give 250 mg (88.5%) of product with mp 189—191°. 5

Anal. Calcd for $C_8H_{12}N_4O_5$: C, 39.34; H, 4.95; N, 22.94
Found: C, 39.25; H, 4.86; N, 23.09

15 EXAMPLE 15 15

(A) 1-*O*-Acetyl-2-deoxy-3,5-di-*O*-*p*-toluoyl-*D*-ribofuranose

A mixture of 2-deoxy-3,5-di-*O*-*p*-toluoyl-*D*-ribofuranosyl chloride (15.6 g, 40.0 mmol), mercuric acetate (12.7 g, 40.0 mmol) and tetrahydrofuran (200 ml) was stirred at 25° for 10 hours. The solvent was removed and chloroform was added to the residue. The mixture was extracted with 30% aqueous potassium iodide (four 60-ml portions) and water. The organic phase was dried over magnesium sulfate, filtered and concentrated to a syrup (16.0 g, 97.0%). Crystallization of a portion of the product from cyclohexane-benzene provided pure material with mp 88—91°. 20

Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87
Found: C, 67.23; H, 5.97 25

(B) 1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl- α -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester and 1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic Acid Methyl Ester

A mixture of 1-*O*-acetyl-2-deoxy-3,5-di-*O*-*p*-toluoyl-*D*-ribofuranose (4.54 g, 11.0 mmol), methyl 1,2,4-triazole-3-carboxylate (1.27 g, 10.0 mmol) and bis(*p*-nitrophenyl) phosphate (10 mg) was heated with stirring under diminished pressure for 10—15 min. in an oil bath maintained at 150°. The residue was dissolved in methylene chloride and the solution was filtered, then washed with aqueous sodium hydrogen carbonate and water. The organic phase was dried over magnesium sulfate, filtered, and evaporated to a syrup. Column chromatography of this anomeric mixture over silica gel with chloroform provided the α -anomer which was crystallized from cyclohexane-methylene chloride to give 780 mg of pure product with mp 94—95°. 30

Anal. Calcd for $C_{33}H_{25}N_3O_7$: C, 62.62; H, 5.26; N, 8.76
Found: C, 62.44; H, 5.16; N, 8.64 35

40 Subsequent fractions from the silica gel column contained a mixture of the α and β anomers. These fractions were combined and the mixture was further purified by column chromatography over silica gel with chloroform to provide the β anomer as a syrup.

(C) 1-(2-Deoxy- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide

45 A solution of 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (650 mg, 1.35 mmol) in methanol (20 ml) saturated at 0° with anhydrous ammonia was kept at 25° for 3 days in a sealed pressure bottle. The solvent was removed and the residue was applied to a silica gel column. Elution with ethyl acetate-methanol (9:1) provided 1-(2-deoxy- β -*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide (250 mg, 80.8%) as an amorphous solid. 50

Anal. Calcd for $C_8H_{12}N_4O_4$: C, 42.10; H, 5.30; N, 24.55
Found: C, 41.86; H, 5.12; N, 24.49

(AMBERLITE is a Registered Trade Mark).

the residue was crystallized from acetonitrile-ethanol to provide 5.30 g (95%) of product with mp 177°—179° dec.

Anal. Calcd for $C_8H_{14}ClN_5O_4$: C, 34.35; H, 5.05; Cl, 12.68; N, 25.04
Found: C, 34.39; H, 5.06; Cl, 12.73; N, 24.99

EXAMPLE 11

1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamidoxime

A solution of 3-cyano-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole (3.0 g, 8.52 mmol) and excess hydroxylamine in ethanol (100 ml) was refluxed with stirring for 2 hrs. The solvent was removed and the product was crystallized from aqueous ethanol to provide 2.0 g (90.7%) of the carboxamidoxime with mp 212—214° dec.

Anal. Calcd for $C_8H_{13}N_6O_5$: C, 36.89; H, 4.92; N, 27.23
Found: C, 37.07; H, 5.06; N, 27.02

EXAMPLE 12

1-(β -D-Xylofuranosyl)-1,2,4-triazole-3-carboxamide

A mixture of tetra-*O*-acetyl-D-xylofuranose (12.7 g, 40.0 mmol) methyl 1,2,4-triazole-3-carboxylate (5.08 g, 40.0 mmol) and bis-(*p*-nitrophenyl) phosphate (50 mg) was heated under reduced pressure for 20 min. in an oil bath maintained at 160—165°. The residue was cooled and dissolved in chloroform. The crude product was purified by chromatography on silica gel with chloroform-acetone (20:1). A portion (2.0g) of the purified 1-(2,3,5-tri-*O*-acetyl- β -D-xylofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester was treated for 16 hrs at 25° with methanol saturated with ammonia. The solvent was removed and the residue was crystallized from aqueous ethanol to provide 0.70 g of product with mp 194°—196.5°.

Anal. Calcd. for $C_8H_{12}N_4O_6$: C, 39.34; H, 4.95; N, 22.94
Found: C, 39.18; H, 4.82; N, 22.97

EXAMPLE 13

1-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide

A solution of 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (488 mg, 2.00 mmol) in pyridine (10.0 ml) containing acetic anhydride (1.0 ml) was maintained at 0—5° for 22 hrs. Ethanol (1.0 ml) was added and the solution was stirred at room temperature for 2 hrs. The solvent was removed and water was added to the residue. The mixture was extracted with methylene chloride (three 20-ml portions) and the organic layer was extracted with aqueous sodium hydrogen carbonate and water. The organic phase was dried over magnesium sulphate, filtered, and evaporated to a syrup which was applied to a silica gel column. Elution with chloroform-methanol (19:1) provided the pure product as an amorphous solid (560 mg, 75.6%).

Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13
Found: C, 45.36; H, 4.66; N, 14.90

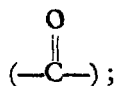
1-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide, when given orally twice daily for 9 days at dosages of 125 and 250 mg/kg/day to mice infected with influenza A₂ (Jap 305), significantly increased the number of survivors as well as the mean survival time of the treated animals relative to control animals.

EXAMPLE 14

1-(β -D-Arabinofuranosyl)-1,2,4-triazole-3-carboxamide

A solution containing methyl N-(trimethylsilyl)-1,2,4-triazole-3-carboxylate (4.12 g, 22.0 mmol) and 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (8.78 g, 20.0 mmol) in anhydrous methylene chloride (100 ml) was kept at 25° for 48 hrs. The solution was evaporated to dryness, the residue was dissolved in methylene chloride and the solution was washed with aqueous sodium hydrogen carbonate and water. The methylene chloride solution was dried over magnesium sulfate, filtered, and concentrated to a syrup which was applied to a silica gel column packed in benzene. Elution of the column with benzene-ether (7:3) provided 1.9 g of syrupy product which was treated with methanol (50 ml) saturated at 0° with anhydrous ammonia in a pressure flask at 25° for 48 hrs. The solvent was removed and the product was crystallized from

was filtered and the filtrate stood at room temperature for two weeks. The resulting precipitate (1.2 g) was dissolved in 5 ml warm water and then 40 ml ethanol was added. The resulting crystals were filtered and dried 12 hours at 78°C over P₂O₅, in *vacuo* to give 1.05 g of 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide 3',5'-cyclic phosphate ammonium salt: α_D²⁵ = 67° (C=1, H₂O); IR (KBr) 1688 cm⁻¹



m.p. 245d.

Anal. Calcd for C₈H₁₁N₄O₅P·NH₃: C, 29.86; H, 4.67; N, 21.47
Found: C, 29.73; H, 4.36; N, 21.66

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EXAMPLE 7

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1-(β-D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide 5'-phosphate
Ammonium Salt

A solution of 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (259 mg, 1.00 mmole), trimethyl phosphate (3.0 ml) and phosphoryl chloride (0.20 ml) were stirred at 0° for 1.5 hrs. Ice water was added and the solution was neutralized with aqueous sodium hydrogen carbonate. The solution was extracted with chloroform and the aqueous phase was cooled to 0° and saturated with ammonia. The solution was kept at 25° for 16 hrs., then it was filtered and the filtrate was concentrated to a small volume. Addition of ethanol gave a precipitate which was dissolved in water and passed through a Bio-Rad AG50W-X2 (NH₄) column (20 ml). Concentration of the fractions containing the nucleotide provided the ammonium salt of 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide 5'-phosphate (190 mg., 53.0%).

Anal. Calcd for C₈H₁₁N₅O₆P·H₂O: C, 26.74; H, 5.05; N, 19.50
Found: C, 26.78; H, 5.23; N, 19.68

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EXAMPLE 8

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1-(β-D-Ribofuranosyl)-1,2,4-triazole-3-thiocarboxamide

A mixture of 3-cyano-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,4-triazole (8.0 g, 22.7 mmole), triethylamine (14.0 ml) and ethanol (200 ml) was stirred at 25° while hydrogen sulfide gas was passed into the solution for 2 hrs. The solvent was removed and the residue was treated with a solution of sodium methoxide (600 mg) in methanol (150 ml) or three hours at 25°. After the solution was neutralized with Bio-Rad AG 50W-X2(H), it was filtered, and the solvent was removed. Crystallization of the product from aqueous ethanol provided 4.5 g (76.1%) of the thiocarboxamide with mp 173—175°.

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Anal. Calcd for C₈H₁₂N₄O₄S: C, 36.92; H, 4.65; N, 21.53; S, 12.32
Found: C, 37.12; H, 4.90; N, 21.26; S, 12.02

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EXAMPLE 9

3-Cyano-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,4-triazole

A mixture of 3-cyano-1,2,4-triazole (9.41 g, 0.10 mol) and 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (31.8 g, 0.10 mol) was heated in an oil bath maintained at 150°. Bis(p-nitrophenyl) phosphate (100 mg) was added with stirring and heating at 150° under diminished pressure was continued for 15 min. The residue was dissolved in chloroform, the solution was filtered and the solvent was removed. Crystallization of the residue from ether provided 28.2 g (80%) of product with mp 96—97°.

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Anal. Calcd. for C₁₄H₁₆N₄O₇: C, 47.73; H, 4.58; N, 15.90
Found: C, 47.79; H, 4.63; N, 15.95

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EXAMPLE 10

1-(β-D-Ribofuranosyl)-1,2,4-triazole-3-carboximidine hydrochloride

A mixture of 3-cyano-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,4-triazole (7.04 g, 20.0 mmole), ammonium chloride (1.07 g, 20.0 mmol) and anhydrous ammonia (150 ml) was heated in a bomb at 85° for 18 hours. After removal of excess ammonia,

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COMPARATIVE ANTIVIRAL ACTIVITY

No.	Compound	Type 1 Herpes VR	Type 2 Herpes VR	Myxoma VR	Pseudo- rabies VR	Vaccinia VR	Adeno VR	Para- influenza VR	Type 13 Rhino VR
1	1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide	1.5, 1.0, 1.2	1.3	1.7	0.0, 0.0	1.0, 0.9	0.5, 0.5	1.0, 1.0, 0.8	0.5
2	Ammonium salt of the 5'-phosphate of 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide	0.7, 0.8	0.9	—	—	0.5	0.0	0.5	0.3
3	1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-thiocarboxamide	1.0, 0.5	—	0.2	0.1	0.3	0.0	0.0, 0.0	0.1, 0.2
4	1-(β -D-Xylofuranosyl)-1,2,4-triazole-3-carboxamide	0.7, 1.2	—	0.95	0.8	0.7	0.1	0.7, 0.8	0.4, 0.5
5	1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamidine hydrochloride	0.8, 1.0	—	1.1	0.6	—	0.1	0.7, 0.8	0.6
6	1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide 3',5'-cyclic phosphate ammonium salt	0.65, 0.8	—	0.7	0.5	—	0	0	0.6, 0.5
7	5-IDU	1.4, 1.0, 1.6	1.8	0.8	0.6	1.3	0.2	0.0	0.0
8	Ara-C	1.2, 1.1	0.8	0.6	0.4	0.8	0.2	0.1	0.1
9	Ara-A	0.7, 1.1	0.6	0.8, 0.8	0.6, 1.1	0.7, 0.9	0.0, 0.0	0.1	0.1

Compound 1 above has been tested in rabbits and hamsters, and at nontoxic doses displays significant anti-HSV keratitis activity. The compound significantly inhibits the development of HSV-induced lesions in moustails when administered locally to the infection. It has also been tested in mice against influenza A2, influenza B and para-influenza 1, with highly significant antiviral activity seen in these experiments. This compound, it should be noted from Table 1 above, displays a spectrum of antiviral activity substantially broader than that exhibited by IDU, Ara-A or Ara-C. In addition to the antiviral activity documented above, 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide has been found to inhibit growth of the bacteria *Pseudomonas aeruginosa* and the fungi *Candida albicans* and *Cryptococcus diffluentis*.

All of compounds (1-6) above exhibited low cytotoxicity and were soluble in aqueous media.

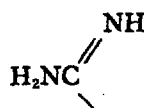
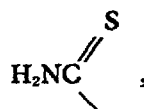
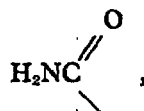
1-(β -D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide also possesses interesting antitumor activity. Three groups of C 57 Blk/6 mice (6 animals per group) were given subcutaneous implants of adenocarcinoma-755. Two groups received the compound (100 mg/kg $\times$ 7 days and 200 mg/kg $\times$ 7 days) intraperitoneally, whereas the third control group received only saline. On the 16th day the treated animals showed 18% and 63% inhibition of the tumor respectively as compared to the controls. In a similar experiment DBA/2 mice inoculated with L-1210 leukemia (1×10^3 cells per animal) showed a 31% increase in median survival time when treated with the compound (250 mg/kg $\times$ 7 days) as compared to control animals. When given at a dosage of 250 mg/kg $\times$ 14 days, the compound produced 80% survivors from swiss mice bearing intraperitoneal implants of Ehrlich ascites carcinoma. Marginal *in vivo* activity against Novikoff hepatoma was also seen.

WHAT WE CLAIM IS:—

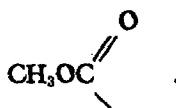
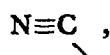
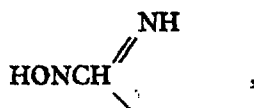
1. A compound of the formula



wherein G is a furanosyl moiety and R₁ is



or a physiologically acceptable acid addition salt thereof,



or

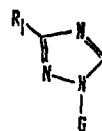
Compound 1 above has been tested in rabbits and hamsters, and at nontoxic doses displays significant anti-HSV keratitis activity. The compound significantly inhibits the development of HSV-induced lesions in moustails when administered locally to the infection. It has also been tested in mice against influenza A2, influenza B and para-influenza 1, with highly significant antiviral activity seen in these experiments. This compound, it should be noted from Table 1 above, displays a spectrum of antiviral activity substantially broader than that exhibited by IDU, Ara-A or Ara-C. In addition to the antiviral activity documented above, 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide has been found to inhibit growth of the bacteria *Pseudomonas aeruginosa* and the fungi *Candida albicans* and *Cryptococcus diffluentis*.

All of compounds (1—6) above exhibited low cytotoxicity and were soluble in aqueous media.

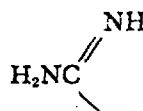
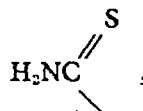
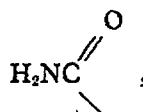
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WHAT WE CLAIM IS:—

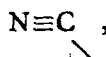
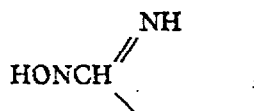
1. A compound of the formula



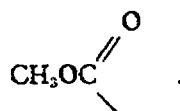
wherein G is a furanosyl moiety and R₁ is



or a physiologically acceptable acid addition salt thereof,



or



* C L M S *



* C L M S *

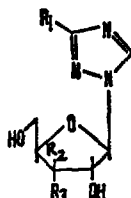
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2. The 5'-phosphate or 3',5'-cyclic phosphate of a compound according to claim 1.
3. A compound as claimed in claim 1 or claim 2 wherein G is a furanosyl moiety whose 2' oxygen in *trans* to the aglycon.
4. A compound as claimed in any one of the preceding claims the nucleoside moiety thereof having the structure:



wherein one of R₂ and R₃ is hydroxyl, the other being hydrogen, and R₁ is as hereinbefore defined.

5. A compound as claimed in claim 4, wherein R₂ is hydrogen.
6. A compound as claimed in claim 4, wherein R₃ is hydrogen.
7. A compound as claimed in any one of the preceding claims wherein otherwise free glycosyl hydroxyls are acyl-blocked.
8. The ammonium or alkali metal salt of a compound as claimed in claim 2 or any one of claims 3 to 7 when dependent on claim 2.
9. The ammonium salt of the 5'-phosphate of 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide.
10. 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide.
11. 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-thiocarboxamide.
12. 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamidine.
13. 1-(2,3,5-tri-O-acetyl- β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide.
14. 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamidine hydrochloride.
15. 1-(β -D-xylofuranosyl)-1,2,4-triazole-3-carboxamide.
16. 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide-3',5'-cyclic phosphate.
17. The ammonium salt of the compound of claim 16.
18. A process for preparing a 1-furanosyl-1,2,4-triazole-3-carboxamide, which process comprises a) forming the trimethylsilyl derivative of methyl 1,2,4-triazole-3-carboxylate by reacting the latter with hexamethyldisilazane, b) reacting the product from (a) with an O-acylated active furanose to form a mixture of an O-acylated 1-furanosyl-1,2,4-triazole-3-carboxylic acid methyl ester and the corresponding 5-carboxylic acid methylester, c) separating the 3-carboxylic acid methyl ester obtained in (b) and, d) subjecting the separated 3-carboxylic acid methyl ester to deacylation and aminolysis.
19. A process as claimed in claim 18, wherein the O-acylated active furanose is an O-acylated halo furanose.
20. A process as claimed in claim 18 or 19 wherein the O-acyl groups of the active furanose are O-benzoyl or O-acetyl groups.
21. A process as claimed in any one of claims 18 to 20, wherein the 1-furanosyl group is a β -D-ribofuranosyl, a xylofuranosyl, a 2'-deoxy- β -D-ribofuranosyl, a 2'-deoxy- α -D-ribofuranosyl, a β -D-arabinofuranosyl, or a 2'-O-methylribofuranosyl group.
22. A process as claimed in claim 18, substantially as hereinbefore described in any one of the pairs of Examples 1 followed by 5A, 3 followed by 5B or 1A followed by 14.
23. A 1-furanosyl-1,2,4-triazole-3-carboxamide whenever prepared in a process as claimed in any one of claims 18 to 22.
24. A process for preparing a 1-furanosyl-1,2,4-triazole-3-carboxamide which process comprises a) fusing together methyl 1,2,4-triazole-3-carboxylate or 3-cyano-1,2,4-triazole with an O-acylated furanose, b) in the case of fusion with methyl 1,2,4-triazole-3-carboxylate deacylating the product from (a) and subjecting it to aminolysis, or, in the case of fusion, with 3-cyano-1,2,4-triazole, reacting the product from (a) with hydrogen peroxide in the presence of aqueous ammonia.
25. A process as claimed in claim 24, wherein the O-acylated furanose is a 1-O-acetyl-tri-O-acylated furanose.
26. A process as claimed in claim 24 or claim 25, wherein the O-acyl groups of the O-acylated furanose are O-benzoyl or O-acetyl groups.
27. A process as claimed in any one of claims 24 to 26, wherein the 1-furanosyl group is, a β -D-ribofuranosyl, a xylofuranosyl, a 2'-deoxy- β -D-ribofuranosyl, a 2'-



* C L M S *

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deoxy- α -D-ribofuranosyl, a β -D-arabinofuranosyl or a 2'-O-methylribofuranosyl group.

28. A process as claimed in claim 24, substantially as hereinbefore described in any one of the combinations of specific Examples, 2 followed by 5A 3 followed by 5B or 9 followed by 5C, or in either one of Examples 12 and 15.

29. A 1-furanosyl-1,2,4-triazole-3-carboxamide whenever prepared in a process as claimed in any one of claims 24 to 28.

30. A process for the preparation of a 1-furanosyl-1,2,4-triazole-3-thiocarboxamide which comprises reacting a 3-cyano-1-(O-acylated furanosyl)-1,2,4-triazole with hydrogen sulphide in the presence of triethylamine and deacylating the resulting product.

31. A process for the preparation of a 1-furanosyl-1,2,4-triazole-3-thiocarboxamide which comprises reacting a 3-cyano-1-furanosyl-1,2,4-triazole with hydrogen sulphide in the presence of triethylamine.

32. A process as claimed in claim 30, wherein the 3-cyano-1-(O-acylated furanosyl)-1,2,4-triazole is obtained by fusing together 3-cyano-1,2,4-triazole with an O-acylated furanose.

33. A process as claimed in claim 30, substantially as hereinbefore described in Example 8.

34. A 1-furanosyl-1,2,4-triazole-3-thiocarboxamide whenever prepared in a process as claimed in any one of claims 30 to 33.

35. A process for the preparation of a 1-furanosyl-1,2,4-triazole-3-carboxamidine which comprises reacting a 3-cyano-1-furanosyl-1,2,4-triazole with ammonium chloride and neutralizing the resulting hydrogen chloride salt to liberate the free carboxamidine.

36. A process for the preparation of a 1-furanosyl-1,2,4-triazole-3-carboxamidine hydrochloride substantially as hereinbefore described in Example 10.

37. A process for the preparation of 1-furanosyl-1,2,4-triazole-3-carboxamidoxime which process comprises treating a 3-cyano-1-pentofuranosyl-1,2,3-triazole with hydroxylamine.

38. A process as claimed in claim 37, substantially as hereinbefore described in Example 11.

39. A process for the preparation of a 1-furanosyl-1,2,4-triazole-3-carboxamidine which comprises reducing a 1-furanosyl-1,2,4-triazole-3-carboxamidoxime.

40. A process as claimed in claim 39, wherein the reduction is effected with hydrogen and a palladium catalyst.

41. A process as claimed in claim 39 or claim 40 wherein the 1-furanosyl-1,2,4-3-carboxamidoxime is prepared in a process as claimed in claim 37 or claim 38.

42. A 1-furanosyl-1,2,4-triazole-3-carboxamidine whenever prepared in a process as claimed in any one of claims 35, 36 or 39 to 41.

43. A 1-furanosyl-1,2,4-triazole-3-carboxamidoxime whenever prepared in a process as claimed in claim 37 or 38.

44. A process for preparing the 5'-phosphate of a compound as claimed in claim 1 in which R₁ is a carboxamido, 3-thiocarboxamido or 3-carboxamidine group which process comprises treating the compound with phosphorus oxychloride in trimethyl phosphate.

45. A process as claimed in claim 44 substantially as hereinbefore described in Example 7.

46. A process for preparing the 3',5'-cyclic phosphate of a compound as claimed in claim 1 in which R₁ is a carboxamido, 3-thiocarboxamido or 3-carboxamidine group which process comprises subjecting the corresponding 5'-phosphate to dicyclohexylcarbodiimide cyclization.

47. A process as claimed in claim 46, wherein the 5'-phosphate is prepared in a process as claimed in claim 44 or 45.

48. A process as claimed in claim 46, substantially as hereinbefore described in Example 6.

49. A compound as claimed in claim 2, whenever prepared in a process as claimed in any one of claims 44 to 48.

50. A process for preparing the ammonium salt of a compound as claimed in claim 2 or claim 49 which process comprises treating said compound with aqueous ammonia.

51. A process as claimed in claim 50 substantially as hereinbefore described in Example 7.

52. An ammonium salt of a compound as claimed in claim 2 or claim 49 whenever prepared in a process as claimed in claim 50 or claim 51.

53. A process for preparing the alkali metal salt of a compound as claimed in



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claim 2 or claim 49 which process comprises subjecting an ammonium salt as claimed in claim 52 to ion exchange.

54. An alkali metal salt of a compound as claimed in claim 2 or claim 49 whenever prepared in a process as claimed in claim 53.

5 55. A method of enhancing the lipid solubility of a compound as claimed in claim 1 or claim 2 which method comprises acylating one or more of the free glycosyl hydroxyl groups of said compound. 5

56. A method as claimed in claim 55, substantially as hereinbefore described in Example 13.

10 57. A method of inhibiting the growth of *Pseudomonas aeruginosa* or the fungi *Candida albicans* and *Cryptococcus diffluentis* which comprises contacting the bacteria or fungi with an effective amount of 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide. 10

15 58. A method of inhibiting the development of tumors in non-human animals which comprises administering an effective dose of 1-(β -D-ribofuranosyl)-1,2,4-triazole-3-carboxamide. 15

59. A method of inhibiting tumor development as claimed in claim 58 substantially as hereinbefore described in Example 16.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.