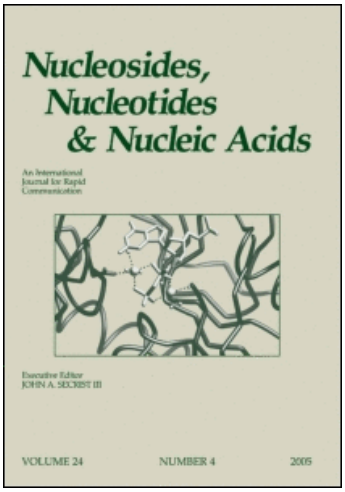

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New Trends in Synthesis of Pyrazole Nucleosides as New Antimetabolites

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NEW TRENDS IN SYNTHESIS OF PYRAZOLE NUCLEOSIDES AS NEW ANTIMETABOLITES

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▫ *Pyrazole nucleosides and condensed pyrazole nucleosides exhibit various biological activities. This article describes recent synthetic approaches to their preparation, chemical properties, biological activities, and structure-activity relationships, with emphasis to selected drugs or drug candidates. Two pyrazole C-nucleoside compounds pyrazofurin (pyrazomycin) and its α-epimer pyrazofurin B are active components of potent antivirals approved for therapeutic use in human medicine aimed against various diseases caused by DNA viruses.*

INTRODUCTION

The incidence of cancer and viral infections has increased dramatically over the past three decades. Consequently, the development of chemotherapeutic agents for cancer and viral infections has been of great scientific interest. In the case of cancer chemotherapy, the effects of the drugs did not only arrest the growth of the tumor, but also destroy various cells of the host. In contrast, with a viral infection, the invader becomes a component of the host cell, actually integrating with and coupling to the cells biosynthetic machinery making it possible to develop a more specific and antiviral agent. Research in cancer and molecular biology, however, has begun to identify certain functions that can be delineated from those of the

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normal host cell and thus become potentially at least amenable to specific chemical interference. One of the most important synthetic strategies in this aspect is chemical modification of nucleosides. Several base-modified nucleosides have been reported to act as antiviral and anticancer agents most likely due to their capability to mimic natural counterparts in structure and function.[1] The synthesis and biological activities of sugar-modified nucleoside analogs have been active research areas for many years since many of these compounds have found useful application in the chemotherapy of cancer and viral infections. A variety of nucleoside derivatives have been prepared through the deletion or change in the nature of the functional group present on the heterocyclic base or their sugar moieties. Such analogs permit the synthesis of oligonucleotides in which a single functional group at a preselected position has been deleted or otherwise altered.

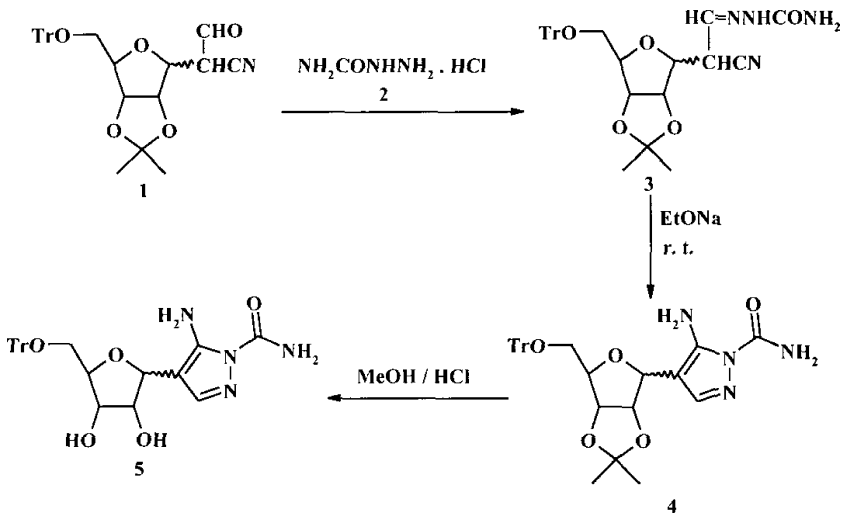
It has been found that some pyrazole nucleosides showed anticancer and/or antiviral activity alone or in combination with other drugs.[2–18] In this study we are concerned with pyrazole and condensed pyrazole nucleosides, as we were involved in synthesizing their analogs. To our knowledge, no attempt to survey their methods of preparation or their wide range of biological applications has been made. The present article fills this gap and involves an up-to-date survey in the synthesis, chemistry, and biological activities of pyrazole and condensed pyrazole nucleosides.

Pyrazole *C*-Nucleosides

Reaction of 2-formyl-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuran-osyl)acetonitrile (**1**) with semicarbazide hydrochloride **2** was followed by sodium ethoxide treatment to afford an α,β-mixture of 3-amino-2*N*-carbamoyl-4-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)pyrazole (**4**). Treatment of compound **4** with methanolic hydrogen chloride gave an α,β-mixture of 3-amino-2*N*-carbamoyl-4-(5-*O*-trityl-D-ribofuranosyl)-pyrazole (**5**). Compound **5** did not show any significant inhibitory action against P815 mouse leukemic cells, although it is an isomer of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICAR), which is a key intermediate not only in the de novo synthesis of purine nucleotides but also in the chemical synthesis of various purine nucleosides[19] (Scheme 1).

It has been found that oxidation of methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**6**) with chromium trioxide and reduction of the resultant aldehyde **7** with sodium borodeuteride gave the labeled ribofuranoside **8**. The deuterated ribose produced by the acid hydrolysis of compound **8** was administered, mixed with (1-^{14}C] ribose, to a *Streptomyces candidus* colony that biosynthesized pyrazofurin **10**[20] (Scheme 2).

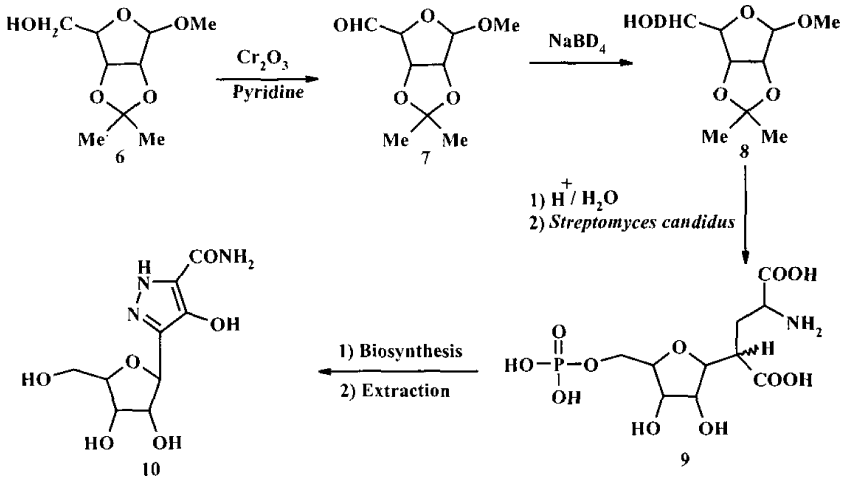
Diazotization of 4-amino-5-cyano-3-(2,3,5-tri-*O*-acetyl-ribofuranosyl)-pyrazole (**11**), and subsequent neutralization with sodium bicarbonate gave the crystalline diazopyrazole **12**. When a solution of **12** was subjected to UV photolysis through pyrex the 4-hydroxy compound **13** was produced. Hydrolysis of the nitrile function gave compound **13**, which, upon deprotection yielded pyrazofurin **10**[21,22] (Scheme 3).



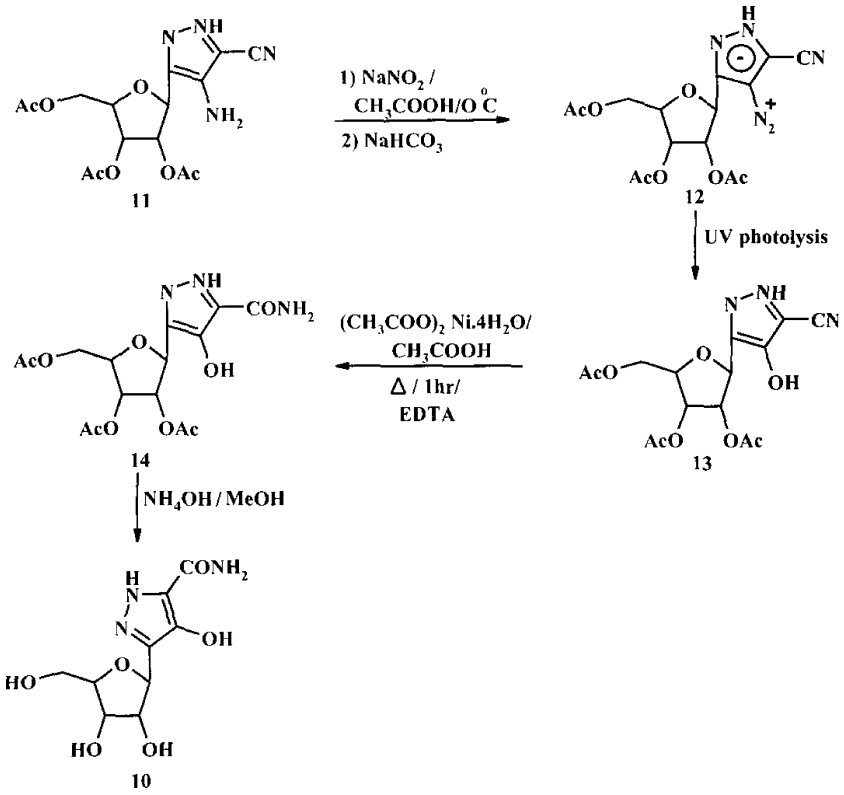
SCHEME 1

Reaction of the protected D-ribose derivative **15** with the phosphorane derivative **16** in acetonitrile afforded compound **17**, which, upon treatment with tosylazide in the presence of triethylamine, afforded the diazo compound **18**. Treatment of **18** with sodium hydride in dimethoxyethane resulted in cyclization to form the pyrazole derivative **19**. Treatment of **19** with methanolic ammonia gave the amide **20**. Deprotection of the latter with 90% trifluoroacetic acid gave pyrazofurin (**10**)[23] (Scheme 4).

The natural *C*-nucleoside pyrazofurin (pyrazomycin) **10a** and its α-epimer pyrazofurin B **10b** are two *C*-nucleoside antibiotics that have generated a considerable

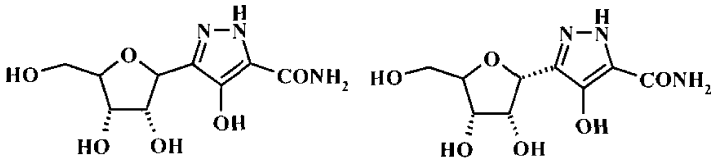


SCHEME 2



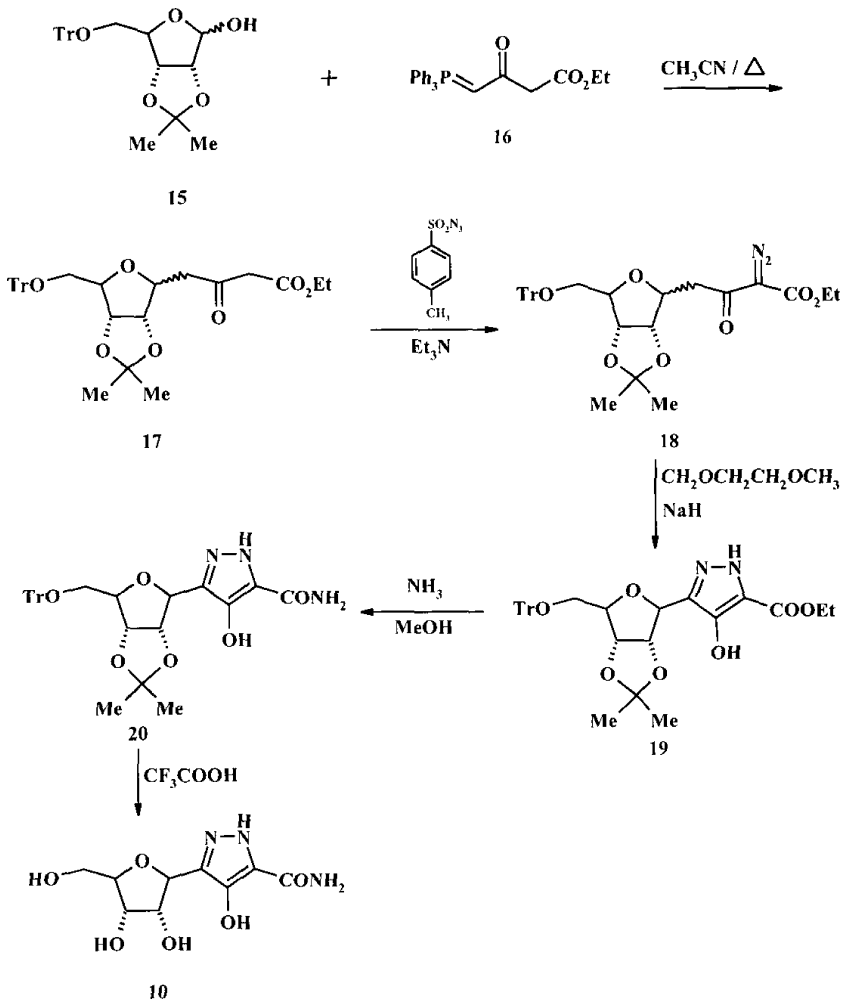
SCHEME 3

interest due to their marked antitumor activities[21–31] and antiviral activity against selected RNA viruses.[27–36] Some tumor cells have been found to show resistance to pyrazofurins.[32] The studies showed that direct binding of hydroxyl group to the pyrazole ring in pyrazofurin-based agents **10a,b** was a must to demonstrate biological activities.[33] Also, pyrazofurin **10a,b** were characterized by a broad spectrum antiviral and antitumor activity at low concentration, but it has a significant toxicity that was reduced when the pyrazole ring was replaced by thiophene ring.[34]



10a
Pyrazofurin (Pyrazomycin)

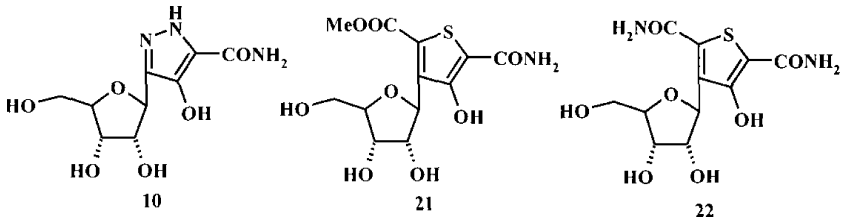
10b
Pyrazofurin B



SCHEME 4

Methyl-5-carboxamido-4-hydroxy-3-(β-D-ribofuranosyl)-2-thiophene carboxylate (**21**) and its corresponding 2,5-thiophene dicarboxamide derivative **22** are two new analogs of the antiviral compound pyrazofurin **10**.[34]

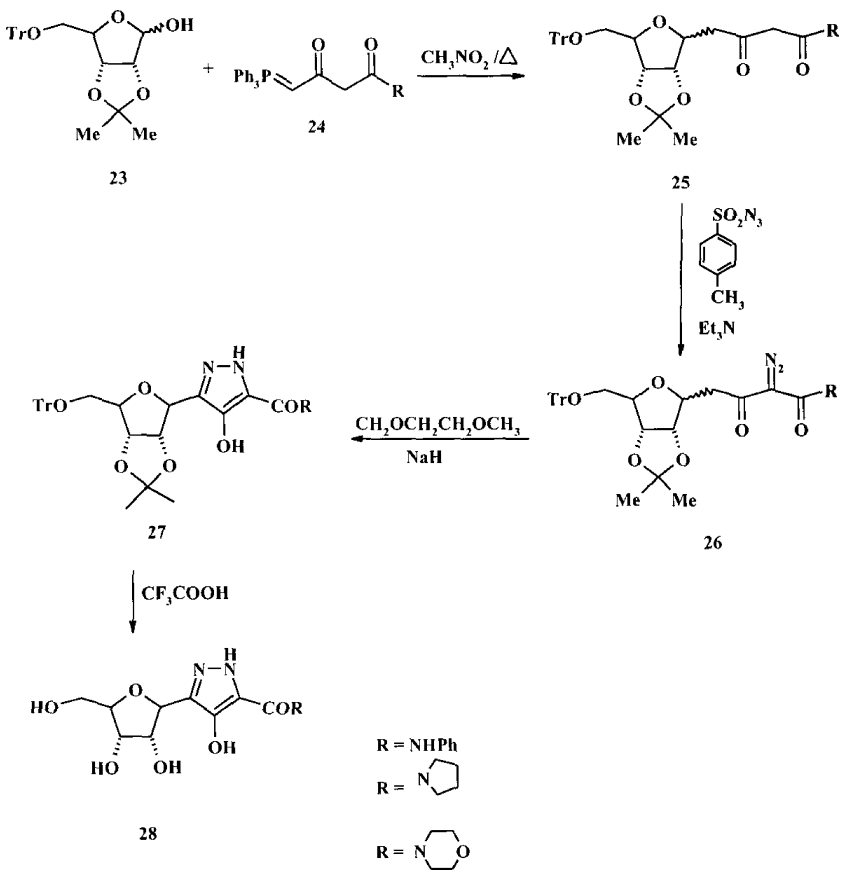
Reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-α and β-D-ribose (**23**) with phosphorane derivative **24** gave compound **25**, then treatment with tosylazide in the



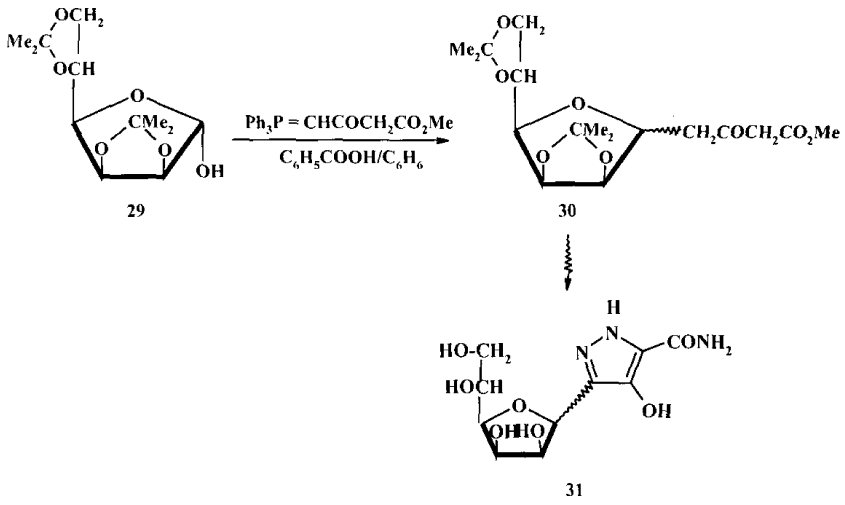
presence of triethylamine afforded compound **26**, which on treatment with sodium hydride cyclized to pyrazole *C*-nucleoside derivatives **27**. The latter upon deprotection afforded the pyrazofurin analogs **28**[35] (Scheme 5).

Reaction of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**29**) with (3-methoxycarbonyl-2-oxopropylidene)triphenylphosphorane was catalyzed by benzoic acid in dry benzene to give methyl 4-(2,3:5,6-di-*O*-isopropylidene-α-and β-D-mannofuranosyl)-3-oxobutanoate (**30**) in good yield. The latter was easily transformed into 4-hydroxy-3-(α-and β-D-mannofuranosyl)pyrazole-5-carboxamide (**31**) (which is the mannofuranosyl analogue of pyrazofurin **10**) through a series of reactions[36] (Scheme 6).

Cycloaddition reaction between ethyl 2-(5-*O*-t-butyl-dimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)propenoate (**32**) and diazomethane yielded the dihydropyrazole **33**. Deprotection of **33** was achieved using aqueous trifluoroacetic acid to yield ethyl 5-β-D-ribofuranosyl-3,4-dihydropyrazole-5-carboxylate (**34**)[37] (Scheme 7).

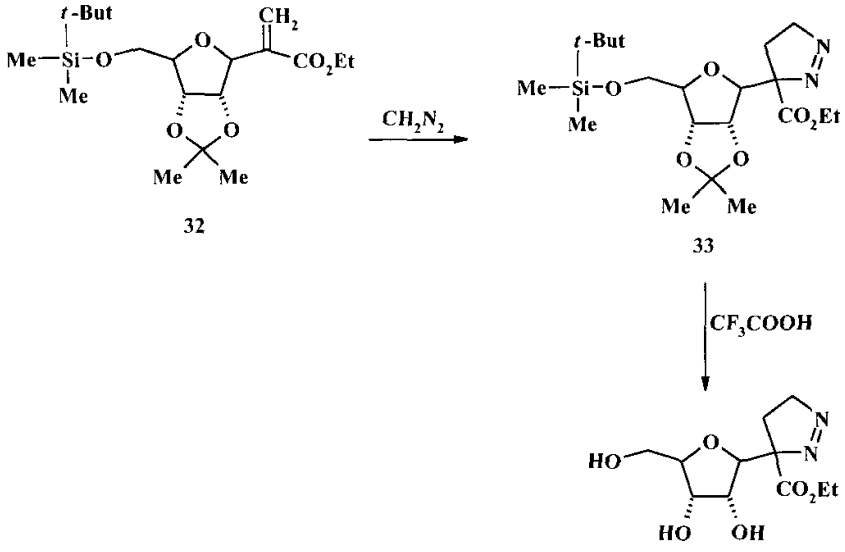


SCHEME 5



SCHEME 6

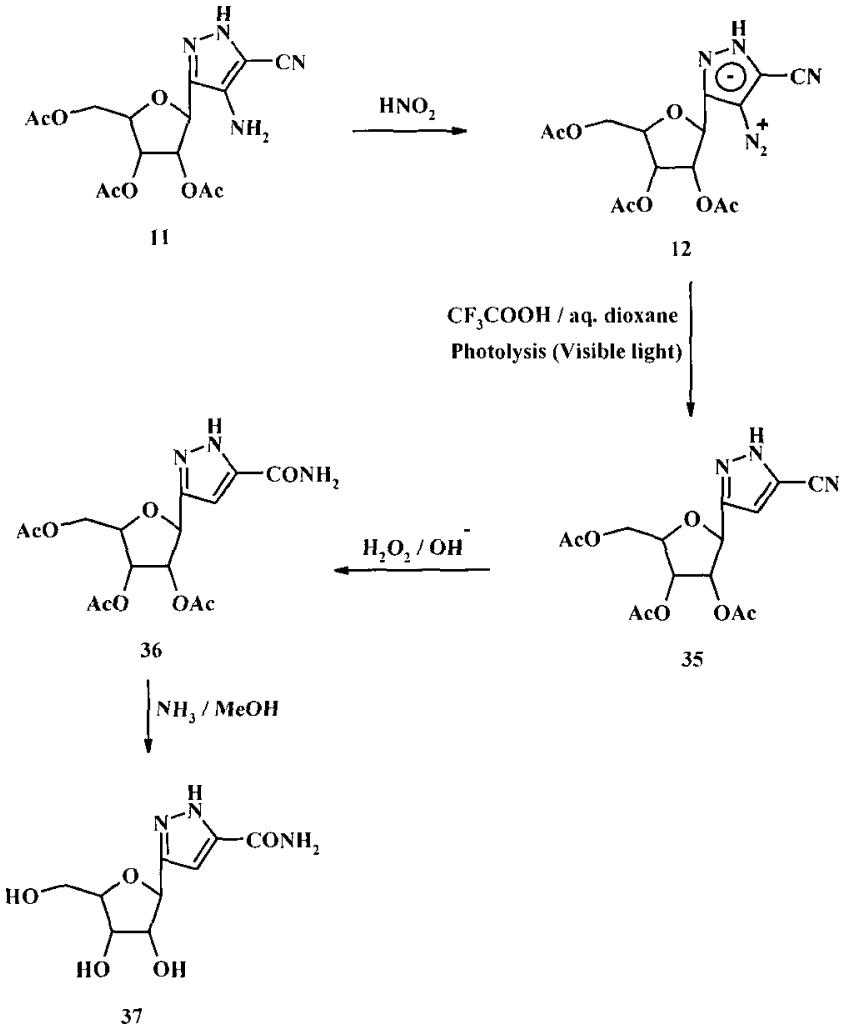
It was found that 4-amino-5-cyano-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole (**11**) was converted into diazopyrazole **12** by treatment with nitrous acid which was dissolved in aqueous dioxane containing trifluoroacetic acid (hydrogen donor solvent). Upon photolysis of **12** by the use of visible light, 5-cyano-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole (**35**) was produced, and this compound formed the corresponding amide **36** on treatment with alkaline hydrogen peroxide. Deprotection of compound **36** with methanolic ammonia afforded 5-carbamoyl-3-β-D-



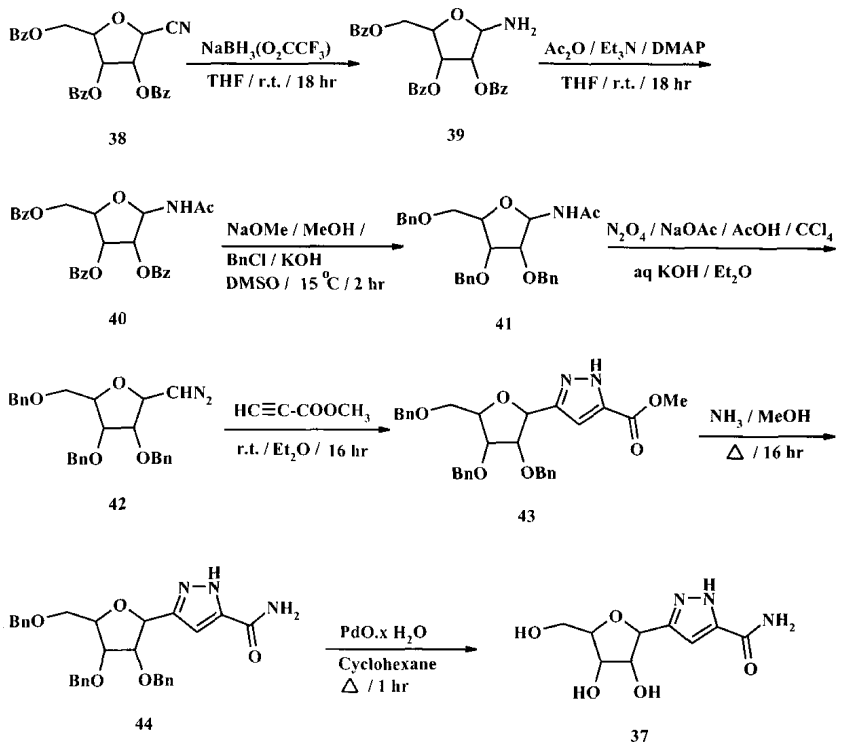
SCHEME 7

ribofuranosyl pyrazole (deoxypyrazofurin) (**37**), which was tested against a wide range of viruses, but it did not show significant antiviral activity[38] (Scheme 8).

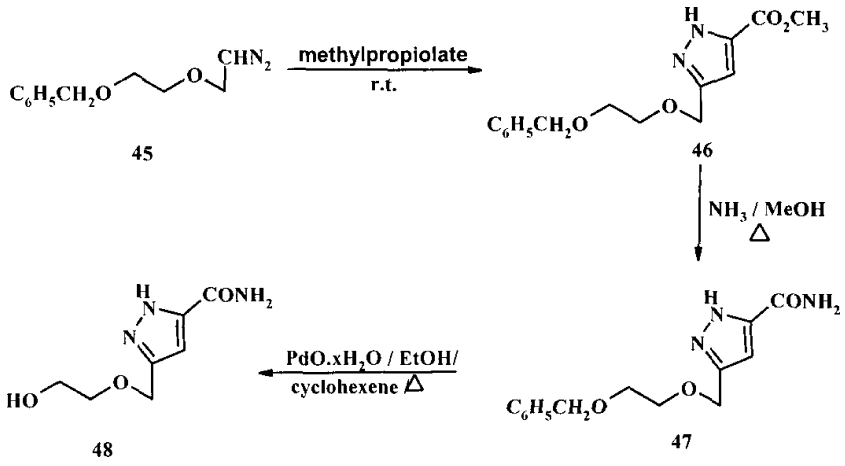
Preparation of 4-deoxypyrazofurin **37** was also reported beginning with 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonitrile (**38**), which was converted through a series of reactions to 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diazo-D-allitol (**42**). A 1,3-dipolar cycloaddition reaction of **42** with methyl propiolate produced the pyrazole nucleoside **43**. Exposure of the latter to methanolic ammonia at 110°C resulted in the formation of the amide **44**. The latter was deprotected with palladium (II) oxide hydrate resulting in the formation of the desired 4-deoxypyrazo-furin **37**, which exhibits low virostatic activity.[39] A survey showed many procedures for the synthesis of 4-deoxypyrazofurin **37**[40–44] (Scheme 9).



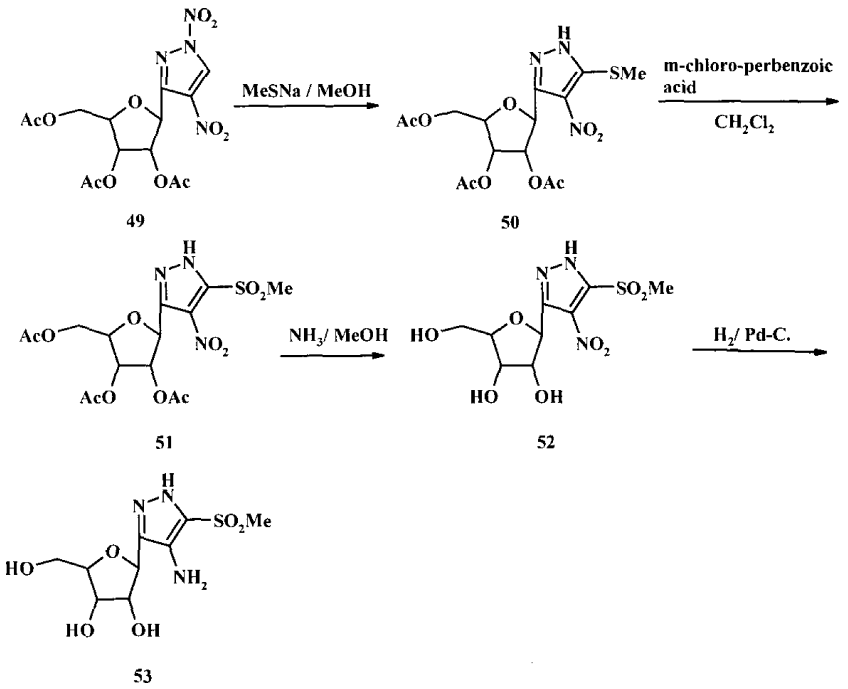
SCHEME 8



SCHEME 9



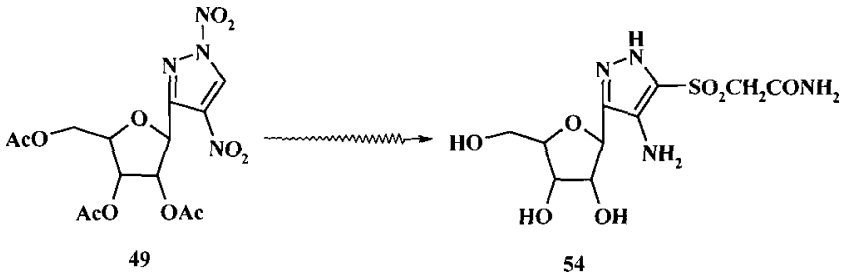
SCHEME 10



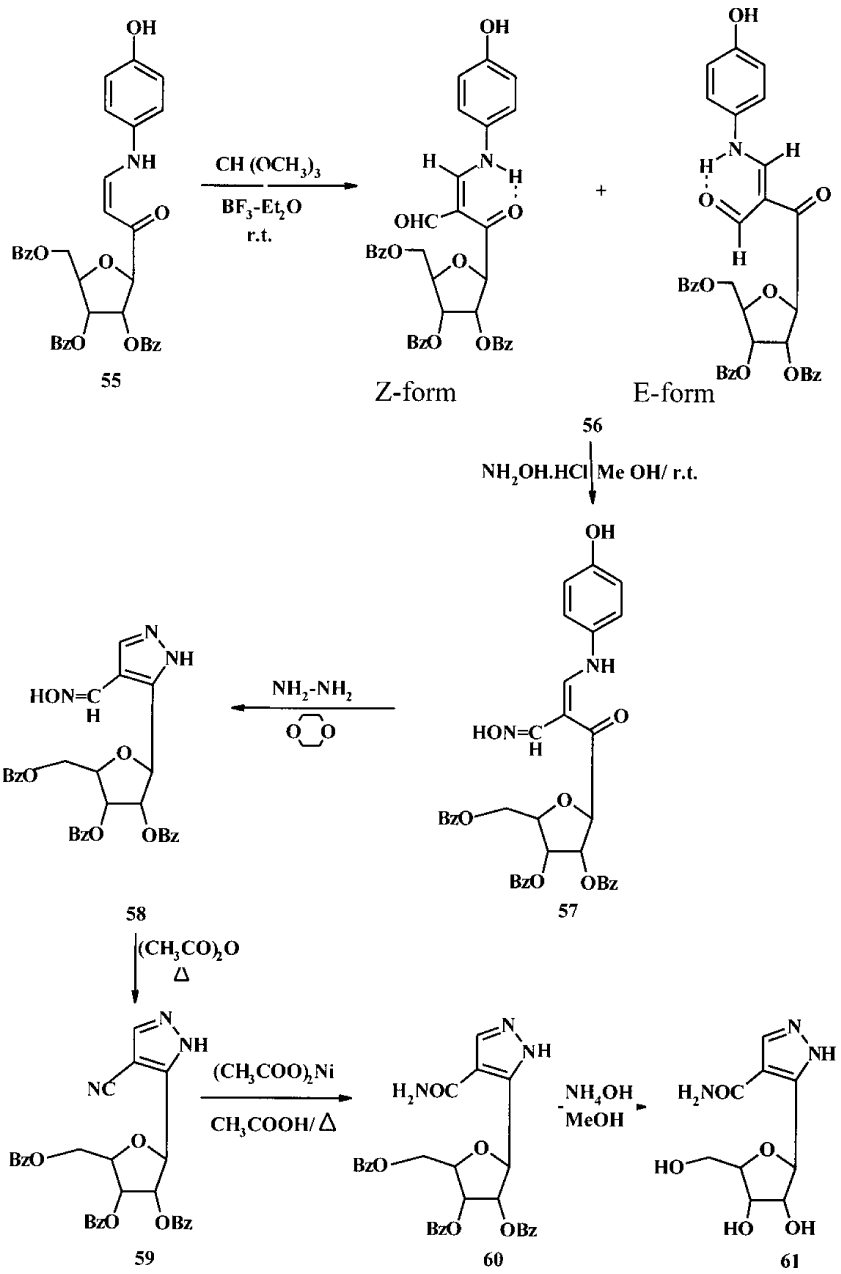
SCHEME 11

1,3-Dipolar cycloaddition reaction of diazoalkane **45** and methyl propiolate gave compound **46**, which upon treatment with methanolic ammonia afforded the corresponding amide **47**. The latter upon hydrolysis gave 3-(2-Hydroxyethoxy-methyl]pyrazole-5-carbox-amide (**48**), which is a nucleoside analog of 4-deoxy-pyrazofurin **37** in which the ribose moiety is replaced by an acyclic residue. It possesses a broad-spectrum antiviral activity[45] (Scheme 10).

Cine-substitution reaction of 1,4-dinitro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole (**49**) with sulfur nucleophiles like sodium methanethiolate in dry methanol and subsequent manipulation led to the synthesis of 4-amino-5-methylsulphonyl-3-(β-D-ribofuranosyl)pyrazole (**53**). Surprisingly compound **53** was unstable to prolonged air storage. The instability of **53** precluded its testing[46] (Scheme 11).



SCHEME 12

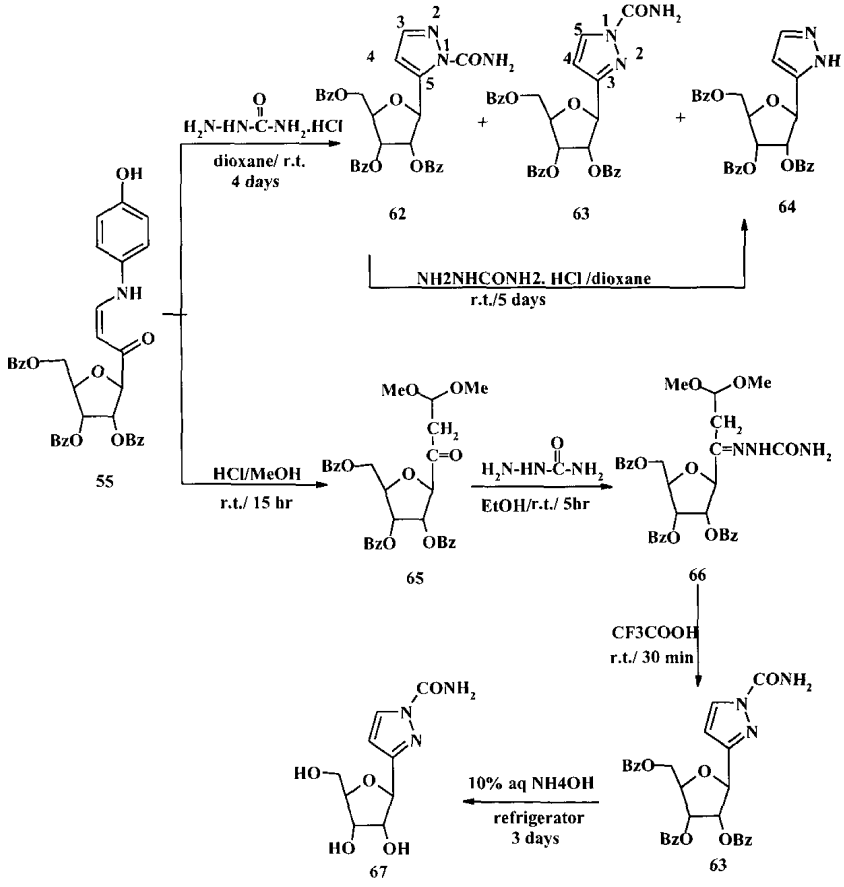


SCHEME 13

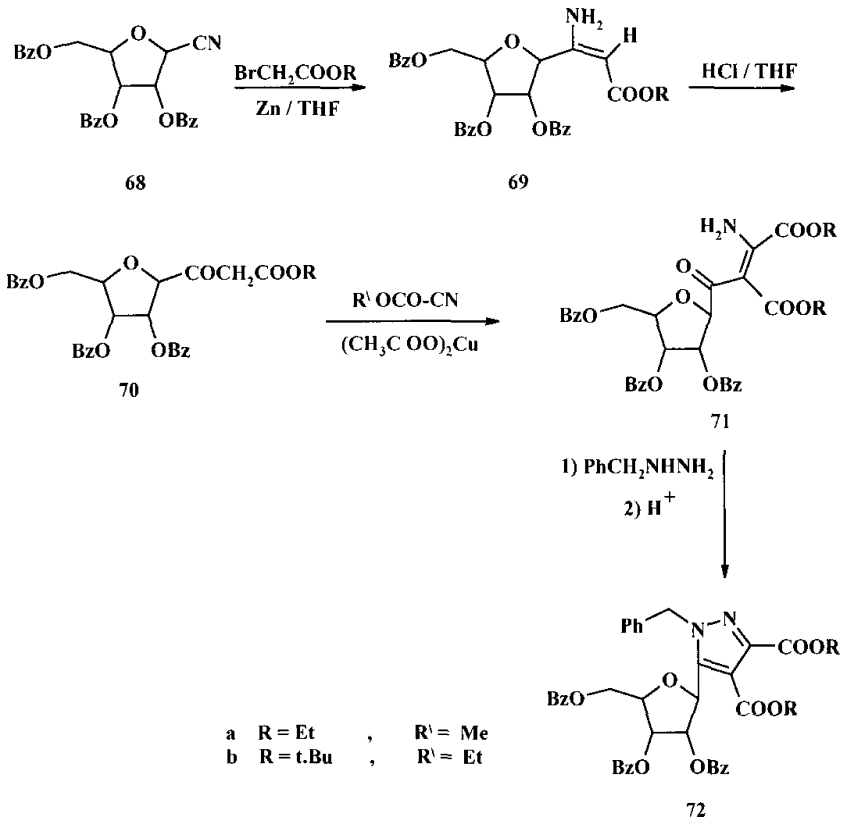
For this reason, 4-amino-5-[carbamoylmethylsulphonyl]-3-(β-D-ribofuranosyl)-pyrazole (**54**) was similarly prepared starting from **49**. Compound **54** did not show significant cytotoxicity against either mouse L1210 leukemia or Walker rat carcinoma cell lines in vitro[46] (Scheme 12).

In view of the known biological activities of several nucleosides bearing carboxamido substituents on the heterocyclic ring, it was of interest to prepare the carboxamide derivative 3-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**61**). Treatment of the enaminone glycoside **55** with trimethyl orthoformate to afforded the aldehyde **56**, which was oximated with hydroxylamine produce compound **57**. Cyclization of **57** with hydrazine afforded the pyrazole derivative **58** that afforded 3-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**61**) through a series of reactions[47] (Scheme 13).

Treatment of the glycosyl enaminone **55** with semicarbazide in dioxane afforded three cyclocondensation products **62**, **63**, and **64**. Compound **62** was

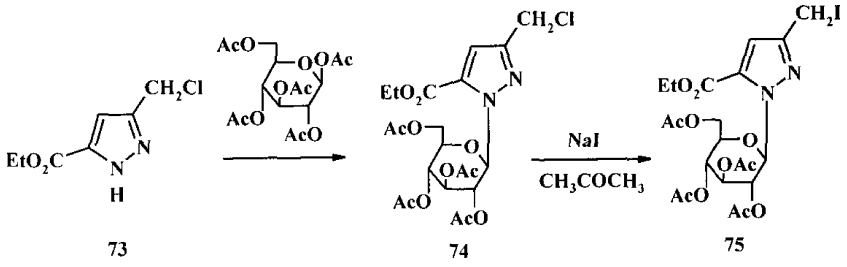


SCHEME 14

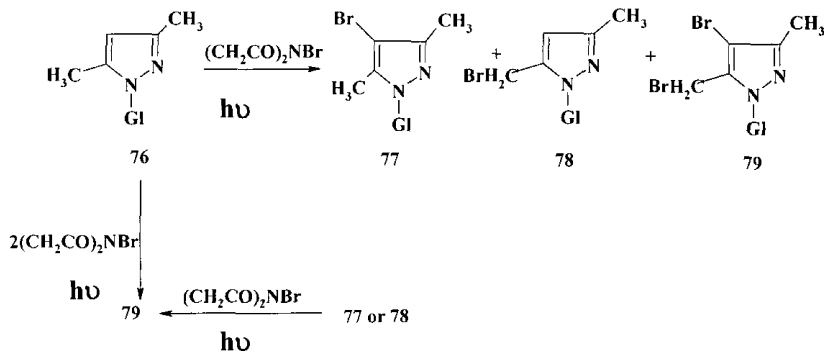


SCHEME 15

gradually converted to compound **64** at room temperature as a result of elimination of the carbamoyl group. Treatment of compound **55** with hydrochloric acid in methanol at room temperature afforded 3,3-dimethoxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-propane-1-one (**65**), which when reacted with semicarbazide afforded the semicarbazone **66**. The latter was cyclized in trifluoroacetic acid to afford **63**. Treatment of **63** with 10% aqueous ammonia gave **67**.[48] The biological



SCHEME 16



a : Gl = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

b: Gl = 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl

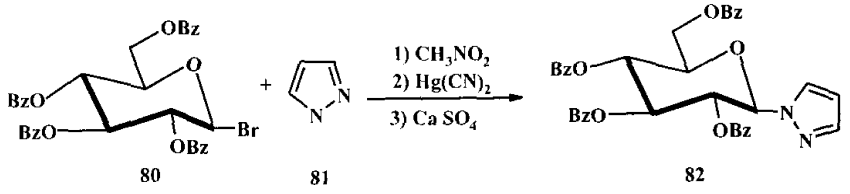
SCHEME 17

effects of compounds **61** and **67** are due to their inhibition of inosine monophosphate dehydrogenase enzyme (IMPDH), which induces the shutdown of guanine nucleotide synthesis[48] (Scheme 14).

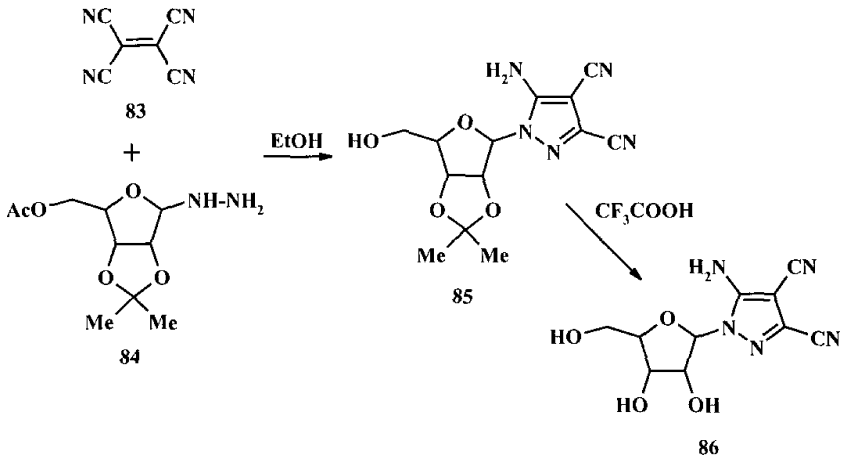
Recently, 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**68**) was reacted with α-bromoesters to give β-D-ribofuranosyl-enaminoesters **69**, which were easily hydrolysed to β-ketoesters **70**. Treatment of the latter with alkyl cyano derivatives afforded *C*-glycosyl enaminoketoesters **71**, which were reacted with benzylhydrazine to give the pyrazole *C*-nucleosides **72**[49,50] (Scheme 15).

Pyrazole *N*-Nucleosides

It has been found that glycosylation of ethyl 3-chloromethylpyrazole-5-carboxylate (**73**) with poly-*O*-acetylated-glucose via an acid catalyzed fusion method gave the corresponding *N*-glycoside **74**. Reaction of the latter with sodium iodide in acetone afforded the corresponding iodomethyl nucleoside **75**. The chloromethyl substituted nucleoside **74** showed moderate activity against HeLa cells, while the corresponding iodomethyl derivative **75** exhibited high activity[51] (Scheme 16).



SCHEME 18

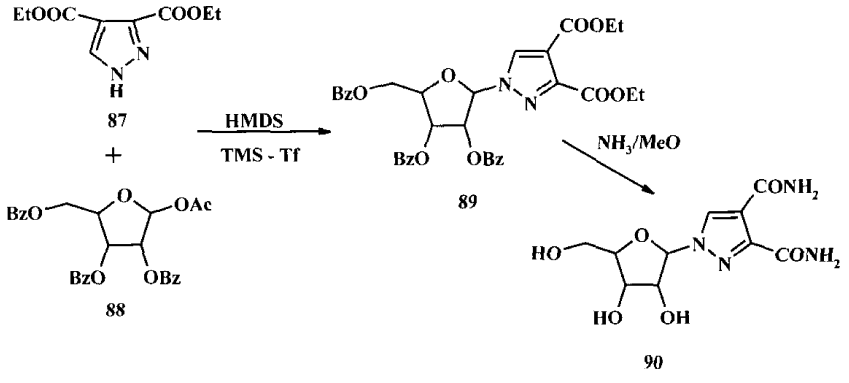


SCHEME 19

Bromination of 3,5-dimethylpyrazole nucleosides **76** with one equivalent of *N*-bromosuccinimide gave a mixture of 4-bromo-3,5-dimethylpyrazole nucleoside **77**, 3-methyl-5-(bromomethyl)pyrazole nucleoside **78** and 4-bromo-3-methyl-5-(bromomethyl)pyrazole nucleoside **79**. On the other hand, bromination of compounds **76** with two equivalents of *N*-bromosuccinimide gave compound **79** only. All of the bromomethylpyrazole nucleosides described showed cytostatic activity against Hela cells[52] (Scheme 17).

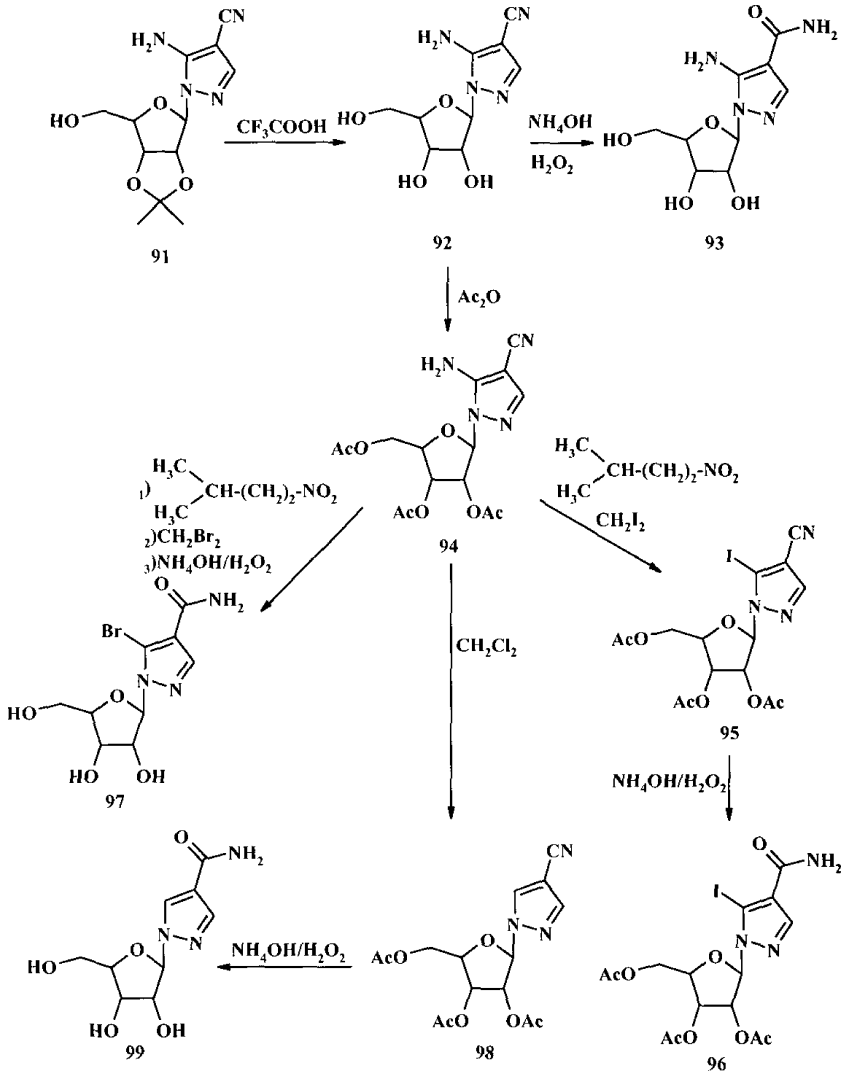
In 1983, a novel procedure for the synthesis of pyrazole *N*-nucleosides was discovered through condensation reaction between 1-bromo-1-deoxy-tetra-*O*-benzoyl-mannose (**80**) and pyrazole **81** in nitromethane, Hg(II) cyanide, and $CaSO_4$ to afford the corresponding tetra-*O*-benzoylated-*N*-glycoside **82**[53] (Scheme 18).

Ring annulation of 1-deoxy-1-hydraziny1-2,3-*O*-isopropylidene-D-ribose (**84**) with tetracyanoethylene **83** gave 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribo furanosyl)-pyrazole-3,4-dicarbonitrile (**85**), which, on deisopropylidination, afforded 5-amino-1-(β-D-ribofuranosyl)pyrazole-3,4-dicarbonitrile (**86**)[54] (Scheme 19).

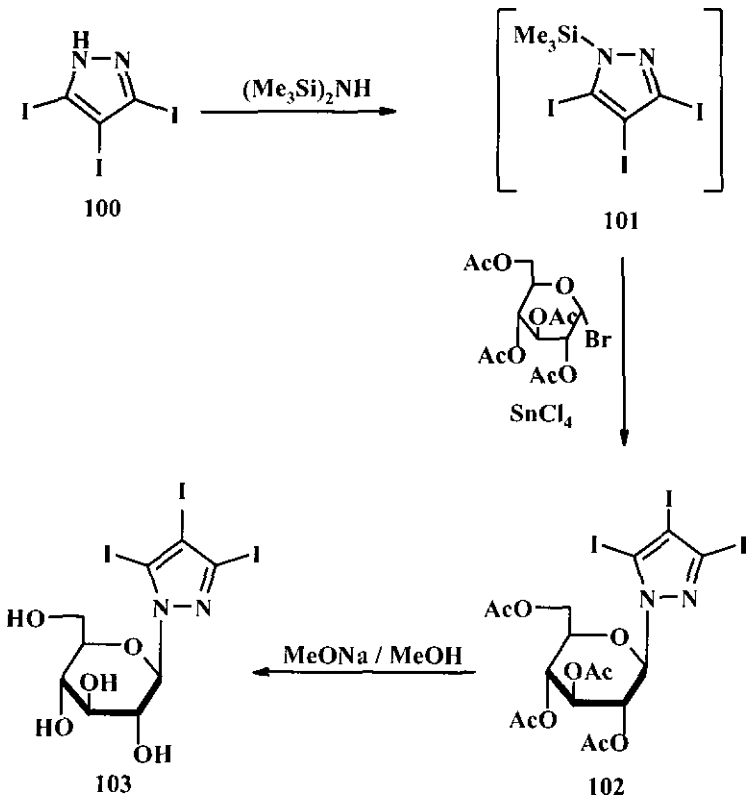


SCHEME 20

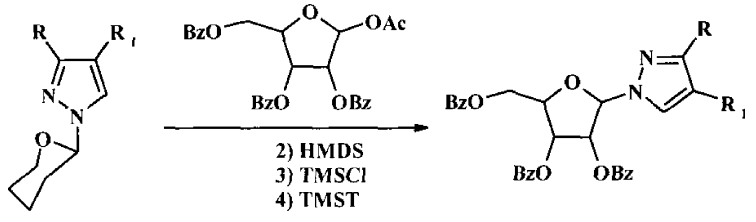
Glycosylation reaction of diethyl pyrazole-3,4-dicarboxylate (**87**) with 1-*O*-acety1-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**88**) gave predominantly the β-nucleoside **89**. Hydrolysis of **89** by methanolic ammonia furnished 1-β-D-ribofuranosylpyrazole-3,4-dicarboxamide (**90**), which was devoid of any significant cytotoxic properties against L1210 and WI-L2 leukemia cells in culture. However, this compound was found to be an inducer of cellular differentiation of HL-60 cells and was comparable to ribavirin in this regard.[54] Also, it inhibited pyrimidine nucleotide biosynthesis in the human myeloid leukemia cell line[55] (Scheme 20).



SCHEME 21



SCHEME 22



R	R'
CO_2Me	I
CO_2Me	CHO
Me	NO_2

SCHEME 23

Deisopropylidenation of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carbonitrile (**91**) gave 5-amino-1-(β-D-ribofuranosyl)-pyrazole-4-carbonitrile (**92**), and conventional hydrolysis of **92** afforded compound **93**. Acetylation of **92** gave **94**. Non aqueous diazotization of **94** with isoamyl nitrite in dibromomethane or diiodomethane gave the corresponding C_5-bromo and C_5-iodo derivatives, which subsequently were transformed into 5-bromo-1-(β-D-ribofuranosyl)pyrazole-4-carboxamide (**97**) and the 5-iodo analog **96**. A similar nonaqueous diazotization of compound **94** in dichloromethane afforded the deaminated product **98**, which, on hydrolysis, gave 1-(β-D-ribofuranosyl)pyrazole-4-dicarboxamide (**99**). Pyrazole nucleosides **91–97** were devoid of any significant antiviral and antitumor activity in vitro[56] (Scheme 21).

3,4,5-Triiodopyrazole (**100**) was silylated with hexamethyldisilazane and then was glucosylated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-bromide to give the β-*N*-nucleosides **102**. 1-(β-D-glucopyranosyl)-3,4,5-triiodopyrazole (**103**) was obtained by treatment of **102** with sodium methoxide in methanol[57] (Scheme 22).

Pyrazole-*N*-tetrahydropyranyl derivatives **104** were converted in one step into the corresponding β-D-2,3,5-tri-*O*-benzoyl-ribofuranosyl nucleoside derivatives **105** by treatment with 1-β-acetyl-2,3,5-tri-*O*-benzoyl-ribofuranose in the presence of hexamethyldisilazane (HMDS), trimethylsilyl chloride (TMSCL) and trimethylsilyl trifluoromethane-sulfonate (TMST)[58] (Scheme 23).

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