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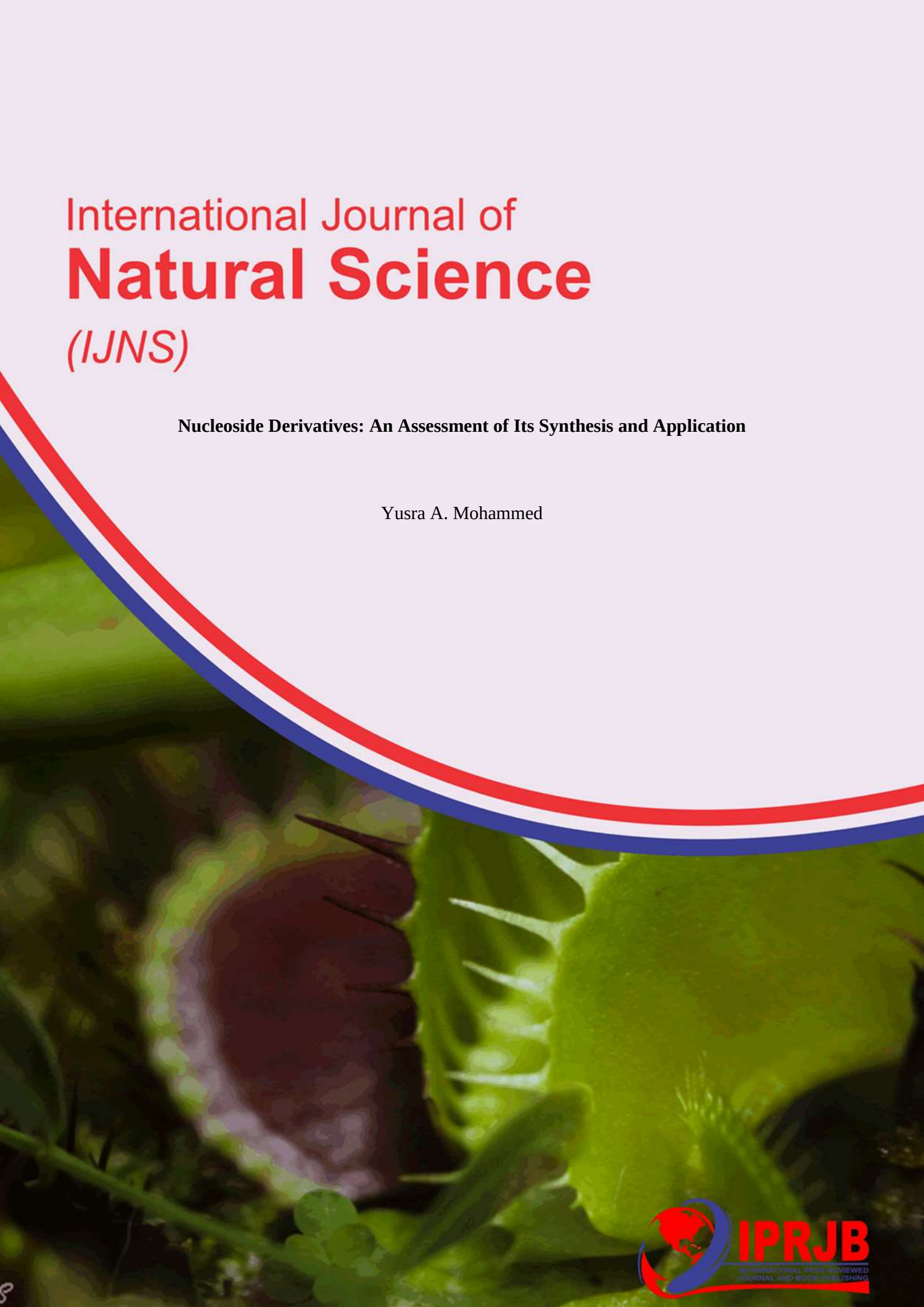

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Nucleoside Derivatives: An Assessment of Its Synthesis and Application

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Abstract

Purpose: This review advances the synthesis methodologies, biological roles, and therapeutic applications of nucleoside derivatives, emphasizing their pivotal role in the development of biomedical sciences.

Methodology: There are several methods for synthesizing nucleosides, including fusion reactions, metal salt procedures, and the Hilbert-Johnson method, each of which offers distinct advantages and challenges. These synthetic approaches take advantage of the interaction of sugars and nitrogenous bases, allowing for tailored modifications for specific applications**.**

Findings: Nucleoside derivatives, essential molecules that are the building blocks of nucleic acids such as DNA and RNA, exhibit diverse structural and functional properties. Their biological synthesis, through novel pathways or rescue mechanisms, ensures the availability of the primary genetic material. Synthetic nucleoside derivatives have found significant roles in medicinal chemistry, particularly in antiviral, anticancer and antibacterial therapies. Modifications of sugars or basic components have led to the emergence of pioneering drugs such as acyclovir, zidovudine and remdesivir**.**

Unique Contribution to Theory, Practice and Policy: Nucleoside derivatives have great therapeutic potential. They act as antiviral agents by disrupting viral replication and as chemotherapeutics targeting rapidly dividing cells in cancers. However, their efficacy faces challenges such as toxicity and development of resistance. Ongoing research aims to enhance their safety and expand their applications in molecular biology, diagnostics and nanotechnology.

Keywords: *Nucleoside Derivatives, Nucleoside Variations, Synthesis Methodologies*

INTRODUCTION

Nucleoside terms are a class of molecules of significant importance that serve as building blocks of nucleic acids such as DNA and deoxyribonucleic acid. These compounds consist of a nitrogenous base generally contributed by a sugar molecule, ribose or deoxyribose.The structural diversity and functional versatility of nucleoside derivatives make them indispensable in a wide range of biochemical and therapeutic contexts. [1]

The biosynthesis of nucleoside derivatives is a critical process in living organisms, ensuring the availability of the raw materials needed for the replication and repair of genetic material. This process involves complex enzymatic pathways that synthesize nucleosides either de novo, starting from simple molecules, or through salvage pathways that recycle pre-existing nucleobases and nucleosides.. [2]

In addition to their biological roles, synthetic nucleoside derivatives have emerged as vital tools in medicinal chemistry, with applications in antiviral, anticancer, and antibacterial therapies. Modifications of nucleoside structure, such as changes to the sugar or base, have led to the development of powerful drugs such as acyclovir, zidovudine, and remdesivir. [3]

Nucleoside derivatives have received significant attention due to their versatility and ability to interact with biological systems. Their applications span antiviral and anticancer therapies, molecular biology research tools, and diagnostic agents. In addition, their use in the design of nanomaterials and bioconjugates further demonstrates their importance.[27]

Nucleoside derivatives are essential to cellular metabolism. They participate in energy transfer (e.g., ATP), signaling (e.g., cAMP), and coenzyme function (e.g., NAD+, FAD). Modified nucleosides are often found in tRNA and rRNA, playing roles in the stability and function of these molecules. Advances in synthetic chemistry and molecular biology continue to open new avenues for the design and application of nucleoside derivatives.[23]

Nucleosides play a crucial role in many biological processes and are essential components of nucleic acids such as DNA and RNA. Beyond their biological importance, they have received significant attention in medicine, particularly in the development of antiviral and anticancer therapies. For example, nucleoside analogues are widely used as therapeutic agents, with applications ranging from the treatment of HIV and hepatitis to certain types of cancer.[24]

Given their importance in therapy, understanding the biosynthesis of nucleosides becomes of paramount importance. This knowledge not only deepens our understanding of cellular processes but also helps in the development of synthetic pathways for medical purposes. Nucleoside biosynthesis is a complex process involving enzymatic pathways that combine nitrogenous base components and sugars. These pathways are tightly regulated within cells, ensuring an adequate supply of nucleosides for nucleic acid synthesis and other cellular functions. Furthermore, advances in biotechnology have enabled the engineering of microbial systems to efficiently produce nucleosides. These breakthroughs are of pivotal importance in addressing the growing demand for nucleoside-based drugs and reducing reliance on chemically intensive synthetic approaches. By first appreciating their therapeutic significance, the exploration of biosynthetic pathways becomes more contextual, emphasizing the direct link between fundamental biological processes and their applications in medicine. [25]

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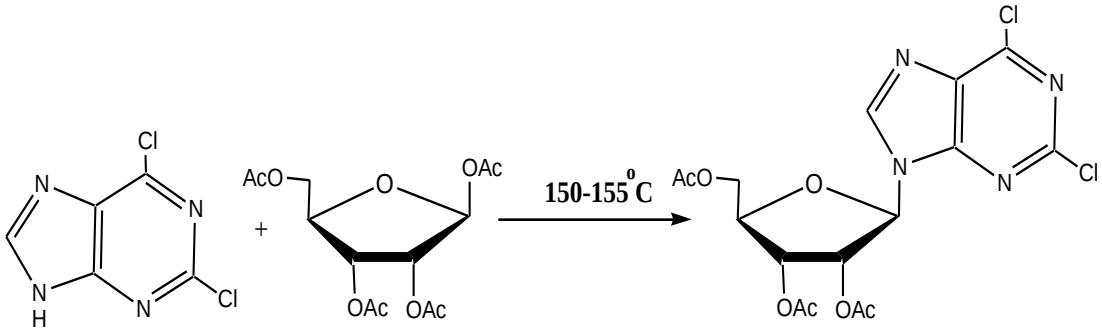
Synthesis of Nucleosides

There are three principal approached methods for the nucleoside forming reactions

The Fusion Reactions

In this reaction [1] a basic heterocyclic system such as 2,6 dichloropurine **(1)**, was heated with a peracetylated sugar **(2)**, (1,2,3,5- tetra-*O*-acetyl-β-ribofuranose) at 150-155^{0}C in melt to yield the nucleoside **(3)**

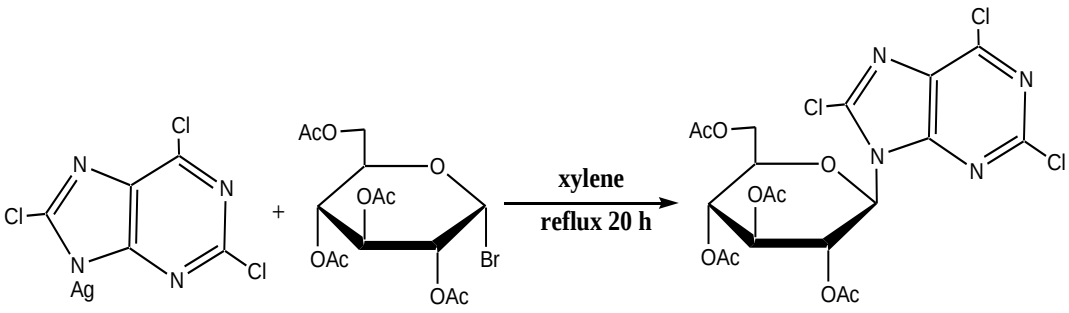


(1) **(2)** **(3)**

The reaction workings with basic systems such as substituted or annulated imidazoles, purines, or pyrazoles. Yields, however, seldom exceeds 60-70%

The Metal Salt Procedure

Metal salts of heterocyclic systems may react with protected sugar halides to yield protected nucleosides.[2] In the original procedure the silver salt of 2,6,8 –trichloropurine **(4)** was heated with 2,3,4,6 tetra-*O*-acetyl-α-D-glucopyranosidyl bromide **(5)** in xylene to give glucopyranoside **(6)**.



(4) **(5)** **(6)**

Davoll *et al*, followed the same method,[3] prepared a number of purine nucleosides ,e.g. the reaction of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride **(7)** with chloromercury-6-acetamidopurine **(8)** in xylene with reflux for 1 h. to yield **(9)** which deacetylated in basic media into adenosine **(10).**

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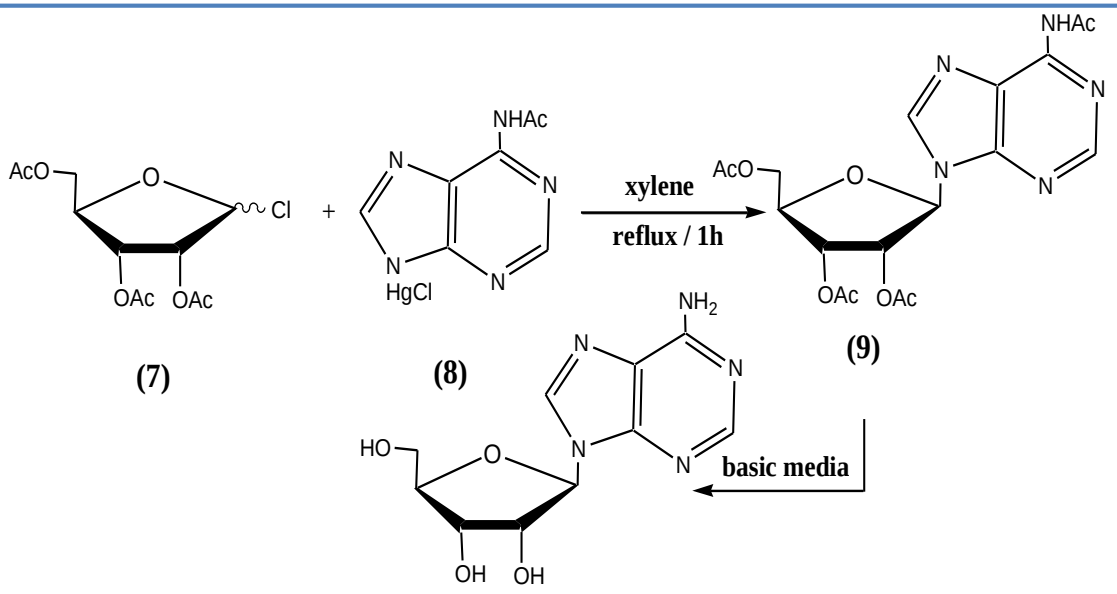
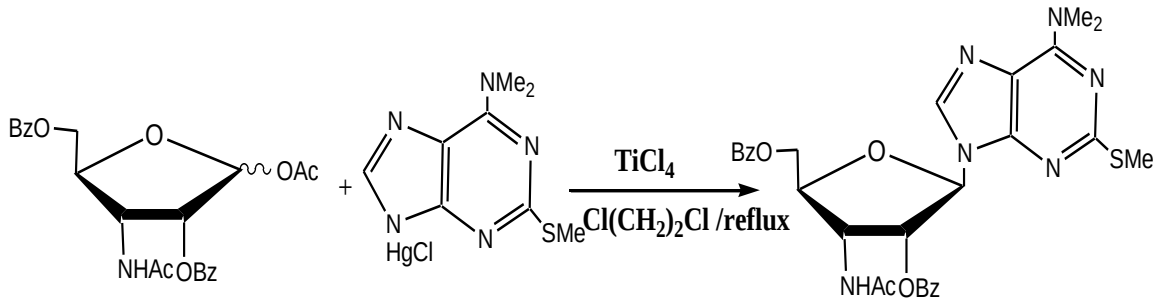


(7) **(8)** **(9)**

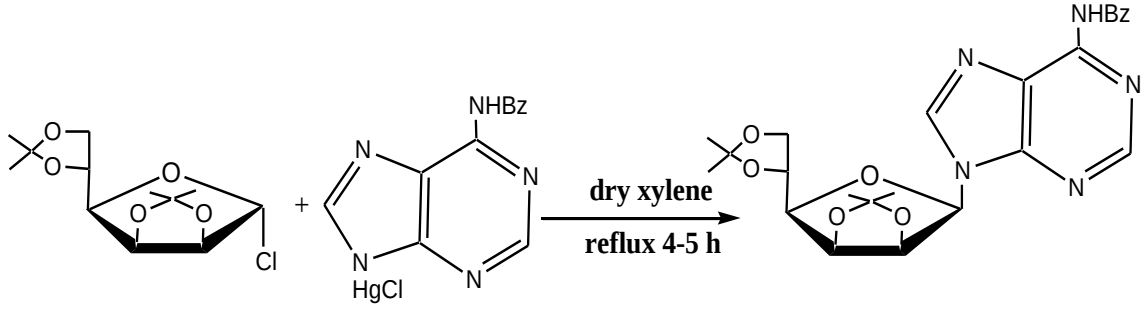
(10)

Baker *etal* prepared [4] 2-mercapto-6-dimethylamino-9-(2`,5` -di-*O*-benzoyl-3`-acetamido-3`-deoxy-β-D-ribofuranosyl)-purine **(13)** by the reaction of sugar derivative **(11)** with purine mercuric salt **(12)** at reflux for 18 h. in ethylenedichloride in presence of $TiCl_4$.



(11) **(12)** **(13)**

The condensation [5]. of 2,3:5,6-di-*O*-isoprpylidene-α-D-mannofuranosyl chloride **(14)** with chloromercuri-6-benzamidopurine **(15)** in dry xylene gave the mannofuranose nucleoside **(16)**.



(14) **(15)** **(16)**

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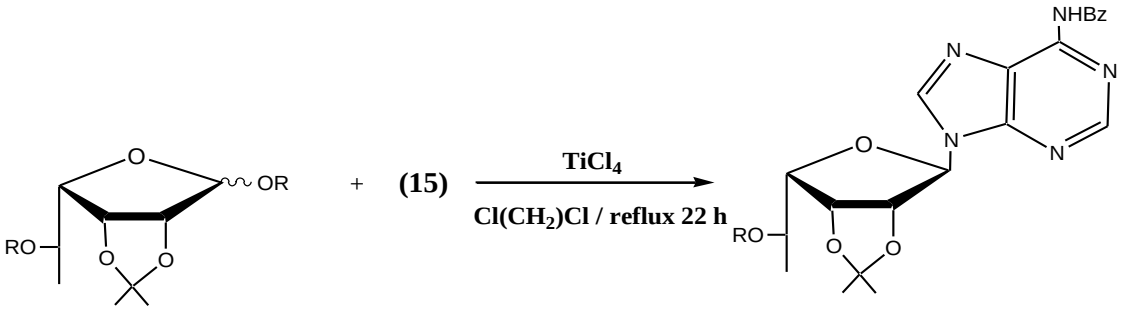
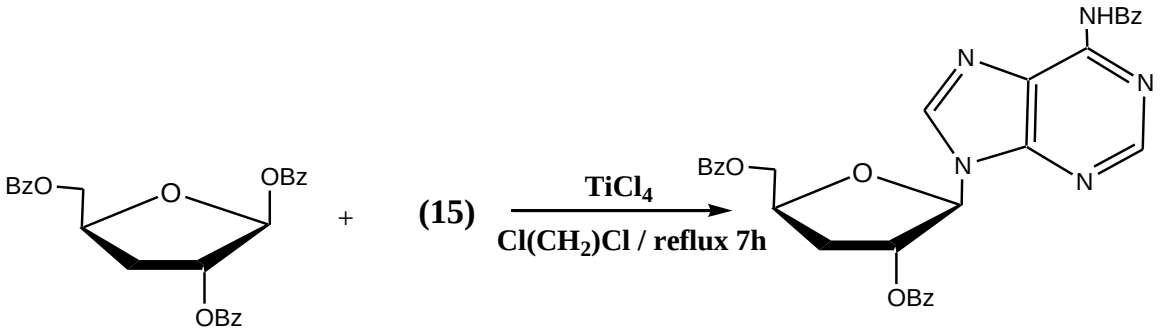
It is not always probable to introduce a halide selectively at the C-1 of an aldose, for example, when the anomeric hydroxyl is already blocked by benzoyl group necessitating it's selective removal before a chloride could be substituted for it. This required because isopropylidene sugars are generally unstable under the usual conditions of glycosyl halide synthesis. [6]

The 1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-rhamnofuranose **(17)** or 1,5-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-rhamnofuranose **(18)** [7] were coupled with compound **(15)** using $TiCl_4$ to yield the corresponding nucleosides **(19)** and **(20)**



R=Ac=(17) and (19)
R=Bz=(18) and (20)

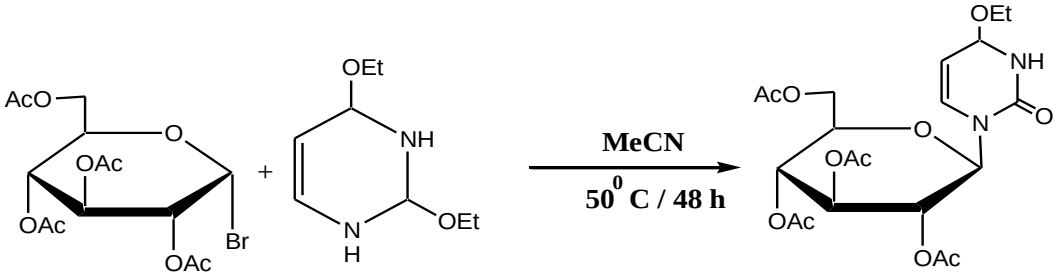
The same above conditions and the nitrogen base salt were used to synthesize the nucleoside **(22)** from its sugar derivative **(21)** [8]



(21) **(22)**

The Hilbert-Johnson method

Hilbert and Johnson reacted 2,4-diethoxypyrimidine **(23)** and sugar bromide **(5)** to give the nucleoside **(25)** in 30% yield.[9,10]



(23) **(25)**

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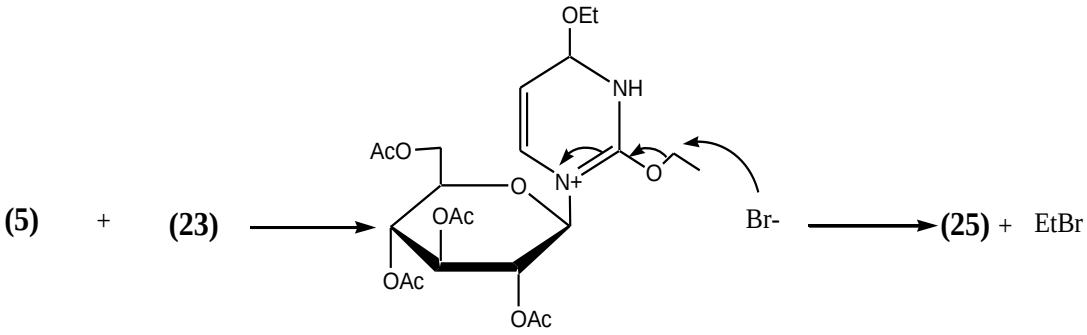
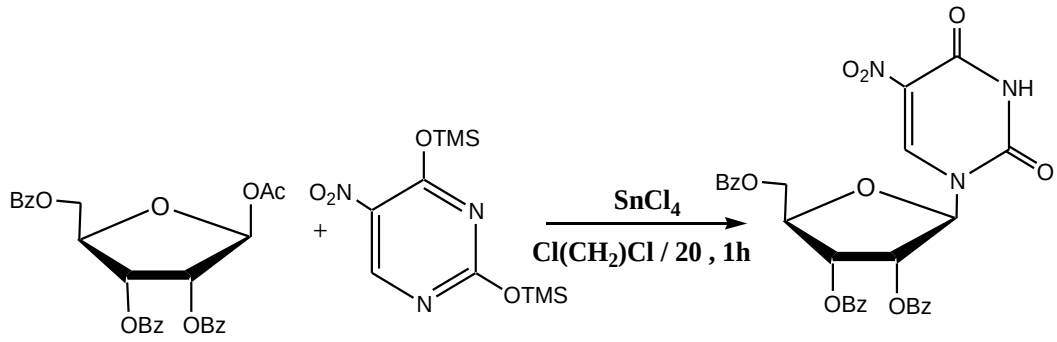
It was postulated that compounds **(5)** react first with **(23)** to give the N-alkylated intermediate **(24)** which then is cleaved by bromide anion to afford[11,12] **(25)** and ethyl bromide



(24)

Birkofer [13,14,15,16] ,Nishimura ,and Wittenburg introduced the silyl-Hilbert-Jhonson reaction.[17] Silylation converts the polar, often rather insoluble pyrimidines bases into lipophilic silyl compounds, which can be distilled and are readily soluble in organic solvents, allowing homogeneous reactions.[18,19] Because of electron-releasing estate of silicon the silylated heterocycles are better nucleophiles than corresponding alkoxyheterocycles. The longer (O-Si) bond of 1.89 A^0 compared to (O-C) bond of 1.53 A^0 make the trimeyhylsilyl groups less bulky than a *tert*-butoxy group and results in the rapid solvolysis of remaining 4-O-trimethylsilyl group

Niedballa [20] synthesized 2`,3`,5` -tri-*O*-benzoyl-5-nitrouridine **(28)** by treating the sugar derivative **(26)** with silylated 5-nitrouracil **(27)** in 1,2- dichloroethne. [20]



(26) **(27)** **(28)**

1-(4`,6` -Di-*O*-acetyl-2`,3` -dideoxy-α and β-D-glucopyranosyl) thymine **(31a)** and **(31b)** have been prepared in a one step one- pot silylation by coupling the glucose derivative **(29)**, [21]with thymine in presence of HMDS and TMSCl in acetonitrile

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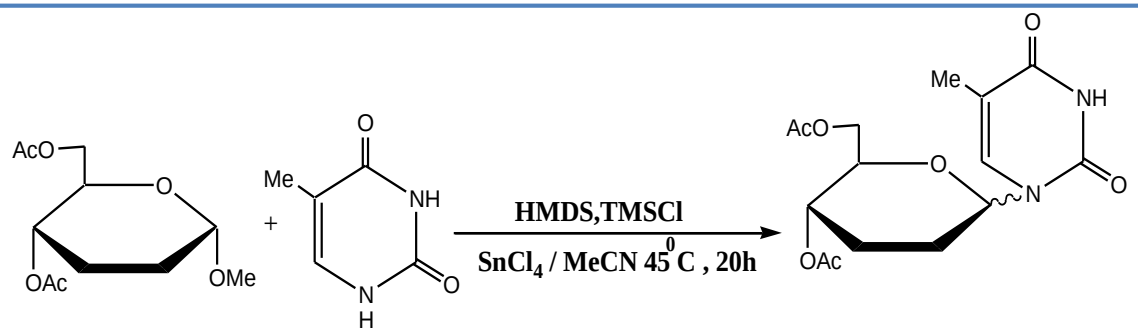
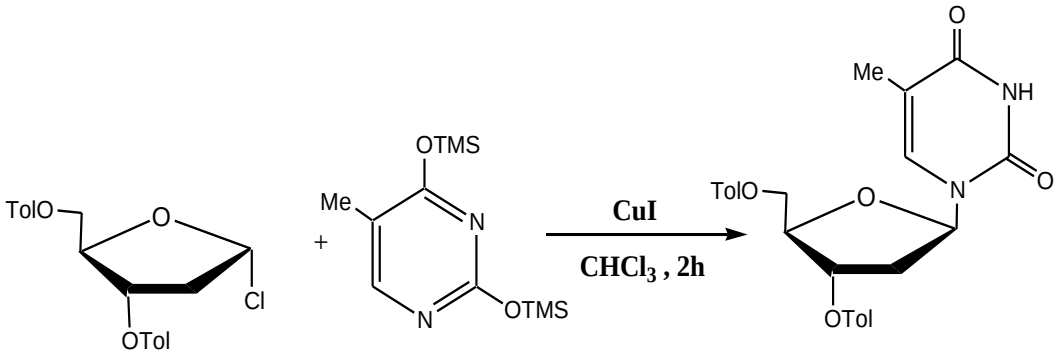


(29) **(30)** **(31a) and (31b)**

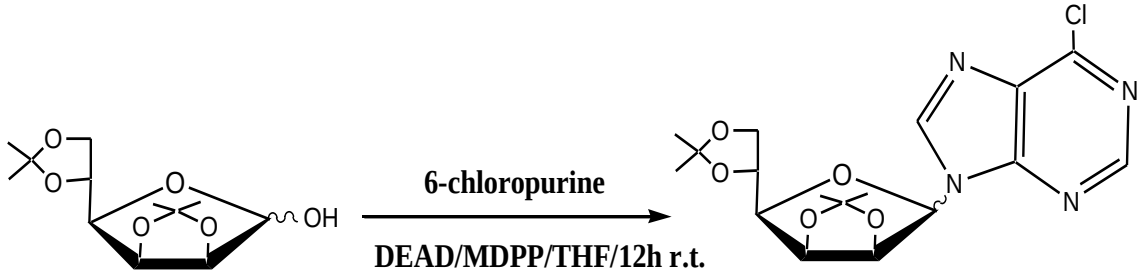
Freskos prepared 3`,5`-di-*O*-toluoylthymidine **(34)** from coupling of the chloride derivative **(32)** with equimolar ratio of bis(trimethylsiloxy) thymine **(33)** in presence of anhydrous copprous iodide.[22]



(32) **(33)** **(34)**

Miscellaneous Methods for Nucleosides Synthesis

A number of methods have been followed for the activation of the anomeric hydroxyl group or building heterocycles attached to the anomeric center of the sugar molecule.
Szarek *etal* [23] synthesized purine nucleosides by a method involving the treatment of an appropriately protected sugar containing a free anomeric hydroxyl group with 6-chloropurine, Diethylazodicaroxylate (DEAD),p and methyldiphenylphosphine (MDPP), e.g., the conversion of 2,3:5,6-di-O-isoprpylidene-D-mannofuranose **(35)** to 6-chloro,9-[2`,3`:5`,6`-di-O-isoprpylidene-D-mannofuranosyl] purine **(36).**



(35) **(36 a & b)**

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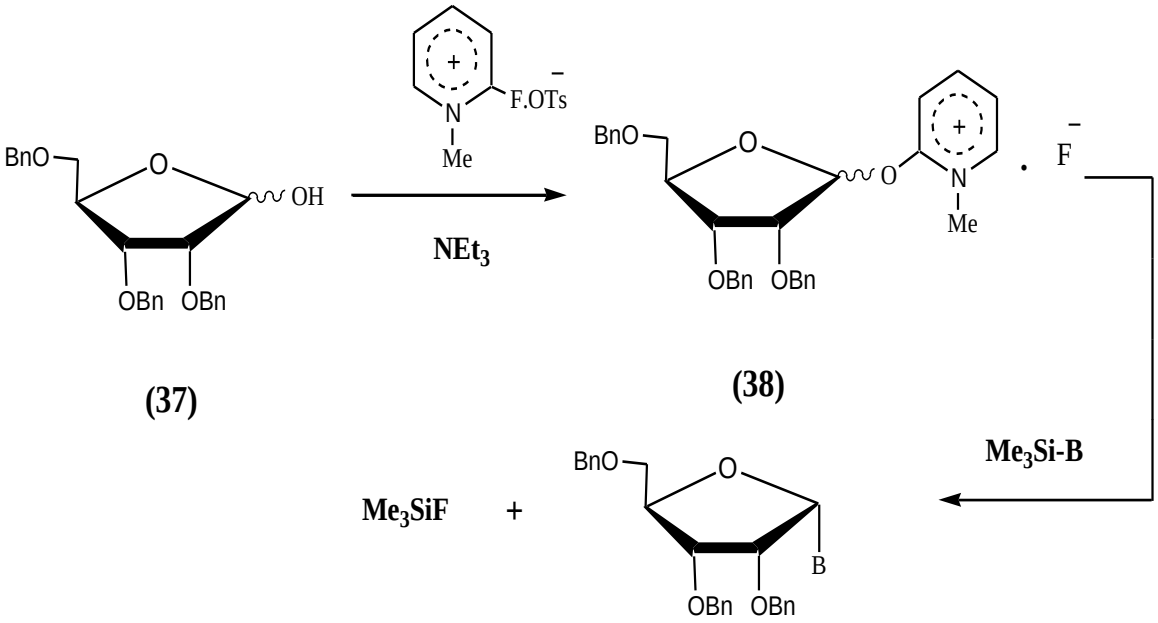
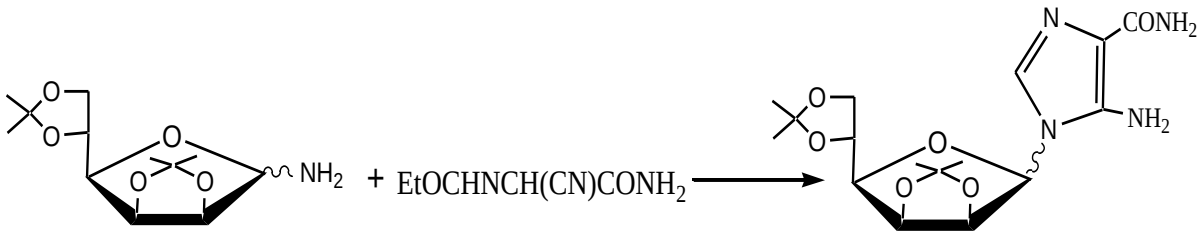
Mukiayama *etal.*[24] have reported an efficient method for the preparation of α-ribonucleosides starting from 1-hydroxyribofuranoses and silylated nitrogen bases using 2-fluoropyridinium tosylate as a condensating agent.



(37) **(38)** **(39)**

The reaction[25] of 2,3:5,6-di-O-isoprpylidene-D-mannofuranosyl amine **(40)** with N-[carbamoyl(cyano)methyl] formimidate **(41)** gave 5-amino-1-(2,3:5,6-di-O-isoprpylidene-D-mannofuranosyl) imidazole-4-carboxamide **(42)**



(40) **(41)**

The reaction[26] of compound **(35)** with (3-methoxycarbonyl-2-oxopropylidene) triphenylphosphorane, gave compound **(42)** in good yield, which was transformed by two subsequent steps into the *C*-nucleoside **(43)**.

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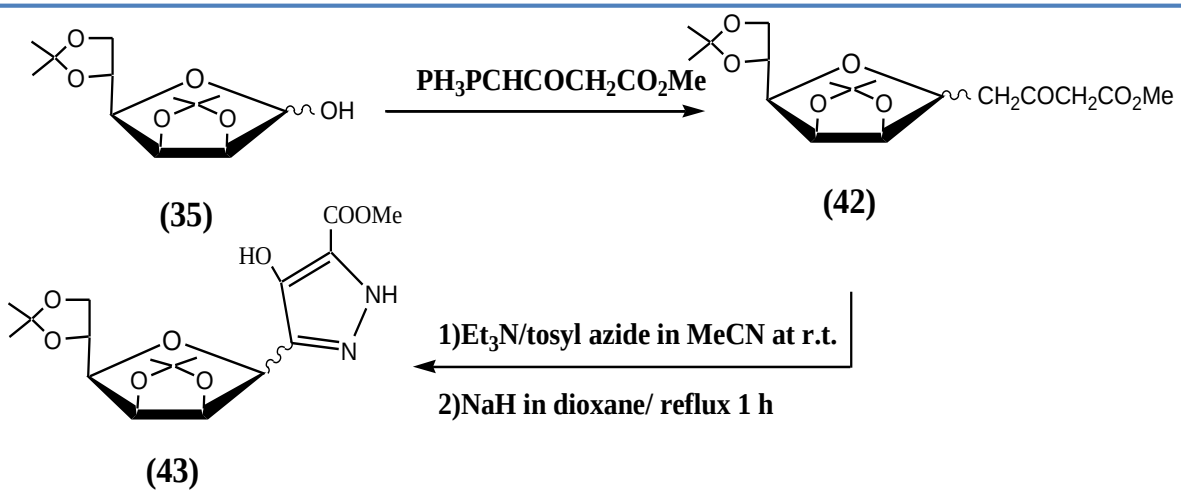
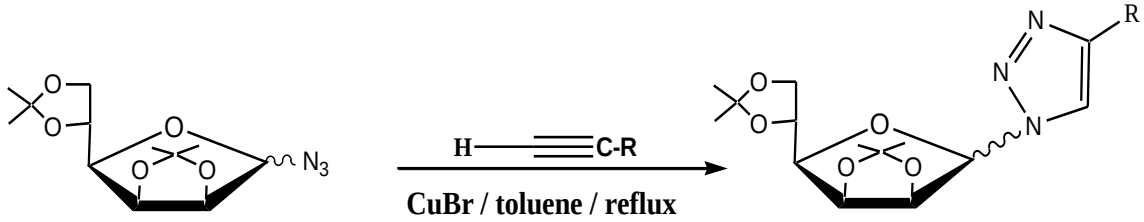


(35) **(42)** **(43)**

Also, nucleosides can be prepared *via* the cycloaddition of terminal alkynes to glycosyl azides in the presence of Cu (I) catalysts to generate the 1,4-disubstituted triazoles, e.g. the reaction of mannosyl azide **(44)** with different terminal alkynes gave the corresponding triazoles **(45)**.



(44) **(45)**

Nucleoside derivatives are structurally modified nucleosides that have garnered significant attention due to their diverse therapeutic applications. These compounds are integral in the treatment of various viral infections, cancers, and other diseases. Nucleoside analogues are pivotal in antiviral therapies. They mimic natural nucleosides, becoming incorporated into viral DNA or RNA during replication, leading to chain termination or faulty genetic material. This mechanism effectively inhibits viral replication. Notable antiviral nucleoside analogues include acyclovir for herpes simplex, lamivudine for hepatitis B, and remdesivir for Ebola and coronaviruses. In oncology, nucleoside derivatives such as gemcitabine and cytarabine are employed as chemotherapeutic agents. [27] They interfere with DNA synthesis in rapidly dividing cancer cells, leading to cell death. These agents are particularly effective in treating certain leukemias and solid tumors. Beyond antiviral and anticancer uses, some nucleoside derivatives exhibit antimicrobial properties. For instance, certain analogues have demonstrated activity against bacterial and protozoal infections, expanding the therapeutic scope of these compounds. The efficacy of nucleoside derivatives stems from their ability to disrupt nucleic acid metabolism. By substituting natural nucleosides, they can inhibit enzymes like DNA polymerases or reverse transcriptases, essential for DNA and RNA synthesis. This disruption hampers the proliferation of viruses, cancer cells, and other pathogens. While nucleoside derivatives are potent therapeutic agents, their use can be accompanied by challenges such as toxicity and the development of resistance. For example, mutations in viral enzymes can lead

to resistance against specific nucleoside analogues. Additionally, side effects like bone marrow suppression may occur due to the impact on mitochondrial DNA. In summary, nucleoside derivatives play a crucial role in modern medicine, offering versatile applications across various therapeutic areas. Ongoing research continues to optimize their efficacy and safety profiles, aiming to overcome existing challenges and expand their clinical utility.[25,28]

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