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SYNTHESIS AND APPLICATIONS OF SUGAR FLUORINATED NUCLEOSIDES

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ABSTRACT

In this review, different methods that have been used for the synthesis of 1'-, 2'-, 3'-, 4'- and 5'-sugar fluorinated nucleosides and their analogous are presented and different fluorinating agents are listed. Highlighted examples of the sugar fluorinated nucleosides that make a great impact on chemistry, biochemistry, and drug discovery are also elaborated. This review has shown that introduction of a fluorine atom in different positions within the sugar structure of the nucleoside improves their reactivity and properties.

Key Words: Nucleosides synthesis and applications, Sugar fluorinated nucleosides, Fluorinating agents

INTRODUCTION

Fluorinated nucleosides attracted many medicinal chemists because of their promising medicinal applications. They play a major role in interrupting the replication of cancer cells or viruses [1-3]. A great intention was given by chemists to the introduction of fluoro group into sugars and nucleosides and different methods for the formation of fluorine carbon bond have been developed [4-7].

It is believed that the inherited biological activity of the fluorine incorporated nucleosides may be due to the electronegativity of fluorine and the strength of the carbon-fluorine bond. Strong electronic character of fluorine can alter the electronic properties of the nucleosides and induce interesting biophysical properties to the sugar-fluorinated nucleosides [8]. They can also be used as building blocks in oligonucleotides [9].

The synthesis of fluorinated nucleosides (by introduction of fluorine atom at 1', 2', 3', 4', and 5' positions) can be achieved, by different fluorinating agents (**Figure 1**), through selective fluorination of nucleosides or by glycosylation of nucleic acids bases (nucleobases) with fluoro-sugar derivatives [10-14].

There are six reported methods for the synthesis of sugar-fluorinated nucleosides (**Figure 2**). These are:

1. Epoxide cleavage by fluoride ions: This reaction has been used for the synthesis of 9-(3-deoxy-3-fluoro-β-**D**-xylofuranosyl) adenine **1** [15], and 9-(3-deoxy-3-fluoro-β-**D**-arabinofuranosyl) adenine **2** [16].
2. Displacement of sulfonyloxy group by fluoride ions: This reaction has been used for the synthesis of 5'-fluronucleosides because displacement of 5'-sulfonates with fluorine is more easily achieved than the same reaction with 2'- or 3'-sulfonates. A good example is the synthesis of 9-(3, 5-dideoxy-5-fluoro -β-**D**-ribofuranosyl) adenine **3** [17].
3. Fluorine anhydro ring opening: This reaction has also been used for the introduction of fluorine in 2'- and 3'-postitions: A good example is the synthesis of 1-(2-deoxy-2-fluoro-β-**D**-ribofuranosyl) uracil **4** [18] and 1-(3-deoxy-3-fluoro-β-**D**-ribofuranosyl) uracil **5** [18].
4. One step exchange of hydroxyl group by fluorine: This has been achieved by treating desired sugar with diethylaminosulfurtrifluoride, **DAST**, or [bis (2-methoxyethyl)-amino] sulfurtrifluoride, **MAST**, then coupling the brominated fluorosugar with the nucleobases [10]. A good example is the synthesis of 9-(2-deoxy-2-fluoro-β-**D**-arabinofuranosyl) purine **6** [10].
5. Sequential photo-bromination and fluorination: In this method desired sugar was treated with *N*-bromosuccinimide, **NBS**, followed by fluorination with silver tetrafluoroborate ($\mathbf{AgBF_4}$) [19]. A good example

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here is the synthesis of 4'-fluoroadenosine **7**.

6. Electrophilic fluorination of the nucleoside 1'-position: in this synthesis treatment of the 1'-lithium enolate, prepared from the 2'-ketoderivative, with N-fluorobenzenesulfonimide (**NFSI**) or 1-Chloromethyl-4-fluoro-1, 4-diazoniabicyclo [2.2.2] octane bis (tetrafluoroborate) (**Selectfluor**) , followed by reduction of the 2'-keto-moeity gave the 1'-fluorouridine derivatives [20, 21]. A good example is the synthesis of 1'-fluorouridine **8** (unprotected nucleosides was not successfully isolated because of the instability.

Although excellent reviews on the synthetic aspects of the fluorinated nucleosides have been published [12, 22], some of them were long and sometimes confusing. Our present review is short, clear and to the point. We tried here to put more emphasis on synthetic methodology and applications of the sugar fluorinated nucleosides.

DISCUSSION

1'- Fluorinated nucleosides

Almost all hydrogens attached to carbons have been substituted by fluorine atoms. However, substitution at 1'-carbon is rarely reported. This is may be due the feeling that 1'-nucleosides are difficult or unstable to synthesize. Recently the synthesis of **protected** 1'-fluoronucleosides (**Scheme 1**) was reported by Shuto group [20, 21].

In this synthesis, treatment of 2'-ketouridine **9** with Lithium bis (trimethylsilyl) amide (LiHMDS) and N-F fluorination agents such as **Selectfluor** or **NFSI** gave anomeric mixture of the 1'-fluoro-2'-ketouridine derivatives **10** and (**Arabino type congener**) in 57-88 % yield. Reduction of the 2'-keto group of **10** by diisobutylaluminiumhydride (**DiBAL-H**) followed by acetyl protection of the resulted hydroxyl group with acetic anhydride ($\mathbf{Ac_2O}$) and 4-dimethylaminopyridine (**DMAP**) gave the 1'-fluorouridine derivatives **11** and **12** (8:9=1:4) in 68 % yield.

This method has three drawbacks:

1. Only protected 1'-fluorouridine derivatives **11** and **12** were isolated and neither isolation nor deprotection and purification of the free 1'-fluoronucleoside was successful. This is may be due to the instability of the deprotected 1'-fluoruridine.
2. This method gives anomeric mixture of protected 1'-fluoruridines and that leads to low yield of the preferred β-anomer.
3. This method was not applied to purine nucleosides.

2'- Fluorinated nucleosides

More attention was given to the synthesis of 2'-β-**D**-fluoronucleosides (**araF**-nucleosides) over the 2'-α-**D**-fluoro nucleosides (**riboF**-nucleosides). This is because of the interesting antiviral activity shown by introducing a fluorine atom at the 2'-β-positions of the nucleosides and nucleoside analogs rather than at 2'-α-positions.

Reichmann et al. [23] and Watanabe et al. [24] developed a synthetic method, in two steps, to obtain 2-deoxy-2-fluor-**D**-arabinose **14a** and 1-bromo-2-deoxy-2-fluoro-**D**-arabinose **14b** from a readily available **D**-glucose derivative **13** (**Scheme 2**). Arabinose sugars **14a-b** were used to synthesize series of fluorinated nucleosides **15-18** in a large scale for biological evaluation. Straightforward method for the synthesis of FIAC and FMAU nucleosides was also developed by Tann *etal.* [25].

For example, 1-(2-deoxy-2-fluoro-β-**D**-arabinofuranosyl)-5-iodocytosine (**FIAC, 15**), 1-(2-deoxy-2-fluoro-β-**D**-arabinofuranosyl)-5-methyluracil (**FMAU, 16**), 1-(2-fluoro-2-deoxy-β-**D**-arabinofuranosyl)-5-iodo uracil (**FIAU, 17**), and 1-(2-fluoro-2-deoxy-β-**D**-arabinofuranosyl)-5-ethyl uracil (**FEAU,18**) have shown potent activity against Herpes Simplex Virus (HSV), and excellent activity against hepatitis-B virus (HBV) and cytomegalovirus (CMV). **FMAU, 16** have also shown significant activity against murine leukemia [22].

Chu's group [26, 27] has also reported an efficient procedure for the synthesis of 1- (2-deoxy-2-fluoro-β-**L**-arabinofuranosyl)-5-methyluracil **21** from sugar **19** (**Scheme 3**).

Another interesting approach is the synthesis of the 2'-fluorinated nucleosides, namely 2'-deoxy-2'-fluoro arabinonucleosides (araF-nucleosides) [28, 29]. They are used as building blocks for the synthesis of 2'-deoxy-2'-fluoro arabinonucleic acid (2'-F'ANA), [30-33] a very promising antisense oligonucleotides. Here the 2'-fluoro nucleosides were prepared via condensation of the silylated nucleic acids bases such as silylated *N*-acetyl cytosine or silylated thymine or *N*-benzoylated adenine with 2-deoxy-2-fluoro-3, 5-di-O-benzoyl-α-**D**-arabinofuranosyl bromide **22**. Deprotection of the produced nucleosides, followed by 5'-tritylation and *N*-benzoylation give araF- nucleosides **23-25** in high yield (**Scheme 4**).

The black sheep of this family of 2'-fluoro nucleosides is the 9-(2-deoxy-2-fluoro-β-**D**-arabinofuranosyl) guanine (araF-G) because the above mentioned procedure yields araF-G in low yields. An efficient synthesis of araF-G has been reported by Elzagheid et al. [29]. It involves coupling of 2-deoxy-2-fluoro-3, 5-di-O-benzoyl-α-**D**-arabinofuranosyl bromide **22** with silylated 2-chloro hypoxanthine **26** to afford 2-chloro-β-araF-I **27** that was transformed in araF-G **28** by treatment with methanolic ammonia in high yield (**Scheme 5**). Another efficient approach for the synthesis of araF-G **28** was reported by Sivets [34]. The synthesis involves reaction

of potassium salts of 2-amino-6-chloropurine with 2-deoxy-2-fluoro-3, 5-di-O-benzoyl-α-D-arabinofuranosyl bromide **22**. In addition to methanolic ammonia, 2-mercaptoethanol and sodium methoxide in methanol was also used to convert the masked nucleoside to araF-G.

In addition to the above mentioned syntheses, a novel synthesis and evaluation of the 5-ethyl analogs of the 2-deoxy-2-fluoro- β -D-arabinofuranosyl nucleosides was reported by Shakya et al. [35]. Among the tested fluorinated nucleosides, the 1-(3-bromo-2, 3-dideoxy-2-fluoro-β-**D**-arabinofuranosyl)-5-ethyluracil has showed promising activity against Mycobacterium tuberculosis and Mycobacterium bovis with no cellular toxicity upto the highest concentration tested (CC_{50} > 100 µg/mL).

A linear synthesis of 2'-deoxy-2', 2'-difluorocytidine (Gemcitabine) was also reported by Brown et al. [36]. Gemcitabine under the trade name Gemzar, by Lilly Company, was widely used as anticancer drug. This linear synthesis involves conversion of 3, 5-di-O-benzoyl-2-deoxy-2, 2-difluororibose to corresponding glycosyl urea followed by conversion to cytosine base thru the uracil derivative.

3'- Fluorinated nucleosides

Carbon-3'-fluoronucleosides have shown a wide range of biological activity [37]. Among them, 3'-deoxy-3'-β-**D**-ribofuranosides of adenine, guanine and their 2-deoxy analogs have shown potent antiviral and cytostatic activities [38].

Synthesis of 3'-fluorinatednucleosides such as 9-(3-deoxy-3-fluoro-β-**D**-xylofuranosyl) adenine **1** [15] and 9-(3-deoxy-3-fluoro-β-**D**-arabinofuranosyl) adenine **2** [16] (**Figure 2**) by reacting 1-(5-O-benzoyl-2,3-epoxy-β-**D**-lyxofuranosyl) adenine with tetraethylammonium fluoride and 1-(5-O-benzoyl-2,3-epoxy-β-**D**-ribofuranosyl) adenine with potassium hydrogen fluoride respectively are subject to few drawbacks. Vigorous reaction conditions are required for the ring opening and strictly anhydrous conditions are needed for the reagent and also to avoid formation of side products. Epoxide ring opening is relatively easy with HF in the presence of tetrahydrofuran or dioxane. This is because of the increased dissociation of the hydrofluoric acid [39].

An alternative route has been reported by Pankiewicz and Watanabe [40] for the synthesis of 9-(3-deoxy-3-fluoro-β-**D**-ribofuranosyl) adenine **33**. This involves the treatment of the nucleoside triflate **29** with sodium acetate to give 3'-O-acetyl derivative **30**. Mild hydrolysis of the later nucleoside in triethylamine-methanol-water mixture gave nucleoside **31** in good yield. Further treatment with DAST [(diethylaminosulfurtrifluoride, Et_2NSF_3] gave the desired 3'-fluorosubstituted nucleoside **32** in high yield. Acidic treatment of **32** with acid gave nucleoside **33** (**Scheme 6**).

Another interesting approach is the synthesis of 3'-fluorinated purine nucleosides **35-37** (**Scheme 7**) from 3'-fluorinated pyrimidine nucleosides **5** and **34** with the application of recombinant T. thermophilus pyrimidine nucleoside phosphorylase (TtpyNP) and E-Coli purine nucleoside phosphorylase (EcPNP) [41].

Another straightforward synthesis of 2', 3'-dideoxy-3'-β-fluoronucleosides was reported by Khalil et al.[42] The 5'-acetyl-3-nitro-2'-deoxynucleodies **38a-b** were reacted with DAST in anhydrous dichloromethane-pyridine mixture to give the corresponding 3'- β -fluoronucleosides. Deprotection of the 3-nitro group was achieved by tributyltin hydride (Bu3SnH) in dry toluene in the presence of α, α'-azoisobutyronitrile (AIBN). Removal of the 5'-acetyl with methanolic ammonia afforded nucleosides **39a-b** (**Scheme 8**).

4'- Fluorinated nucleosides

Another class of the fluoronucleosides that has attention of late is the 4'-fluoronucleosides. They are expected to have significant values in a variety of biochemical studies. A fruitful procedure has been reported by Lee et al. [19] where various 4'-fluorinated nucleosides **42-44** have been prepared in three steps via sequential bromination and fluorination of the ribofuranose **40**. Glycosylation of the 4-fluoro-β-**D**-ribofuranose **41** with *N, O*-bis-(trimethylsilyl) trifluoroacetamide and trimethylsilyl triflate followed by debenzoylation gave the desired fluoronucleosides in good yield (**Scheme 9**).

5'- Fluorinated nucleosides

Four approaches for the synthesis of 5'-fluoronucleosides **45-48** (**Figure 3**) have been reported. These include:

1. Nucleophilic displacement of sulfonates by fluoride ions: This reaction is carried out in either mesylates or tosylates with potassium fluoride in ethylene glycol or with tetrabutylammonium fluoride in dimethylformamide (DMF). However, the use of hydrofluoric acid in dioxane has been reported to give better yields [17].
2. Opening of the O^2, 5'-bond of anhydronucleosides: these anhydronucleosides can serve as good starting materials but they are rarely used [43].
3. Reaction of a free 5'-hydroxyl group with DAST. This reagent has been successfully applied for the replacement of hydroxyl group by a fluorine atom [44].
4. Displacement of iodine as leaving group: In this approach silver fluoride in pyridine has been used for introduction of fluorine atom at 5'-position of the 5'-iodouridine [14].

CONCLUSIONS

In this review, a highlighted number of important synthetic methods of biologically active fluorinated nucleosides have been covered. A fluorine atom, as a mimic of hydrogen or hydroxyl group, that has been introduced in different positions in the sugar moiety of the nucleoside has surely improved their pharmacological and biological properties.

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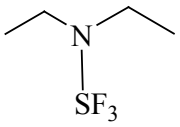

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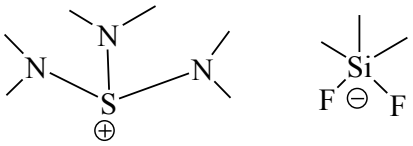
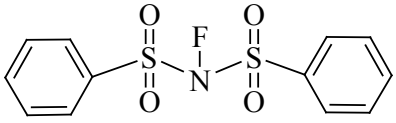
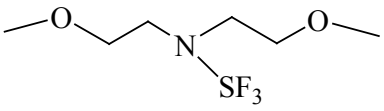
(DAST Reagent)



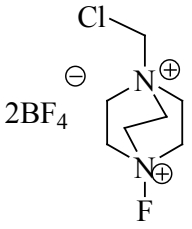
Tris (dimethylamino) sulfonium difluoromethylsilicate
(TASF Reagent)



***N*-Fluorobenzenesulfonimide**
(NFSI Reagent)



[Bis(2-methoxyethyl)-amino] sulfurtrifluoride
(MAST Reagent)



1-Chloromethyl-4-fluoro-1, 4-diazoniabicyclo [2.2.2] octane bis (tetrafluoroborate)
(Selectfluor Reagent)

Figure 1: Fluorinating Agents.

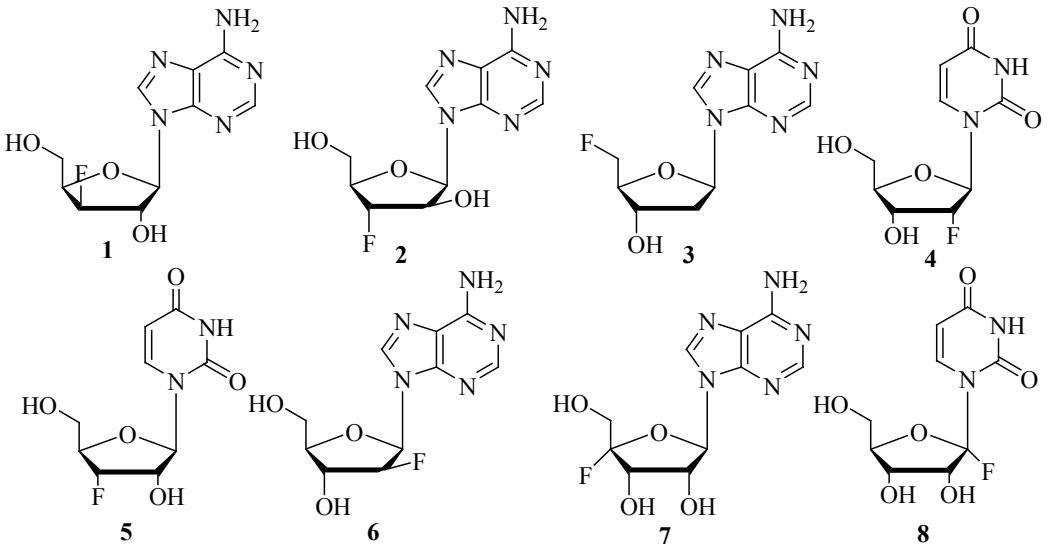


Figure 2: Sugar-Fluorinated Nucleosides.

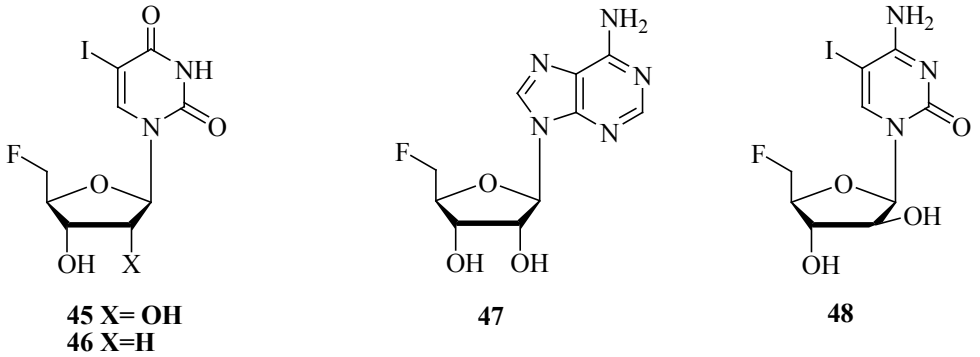
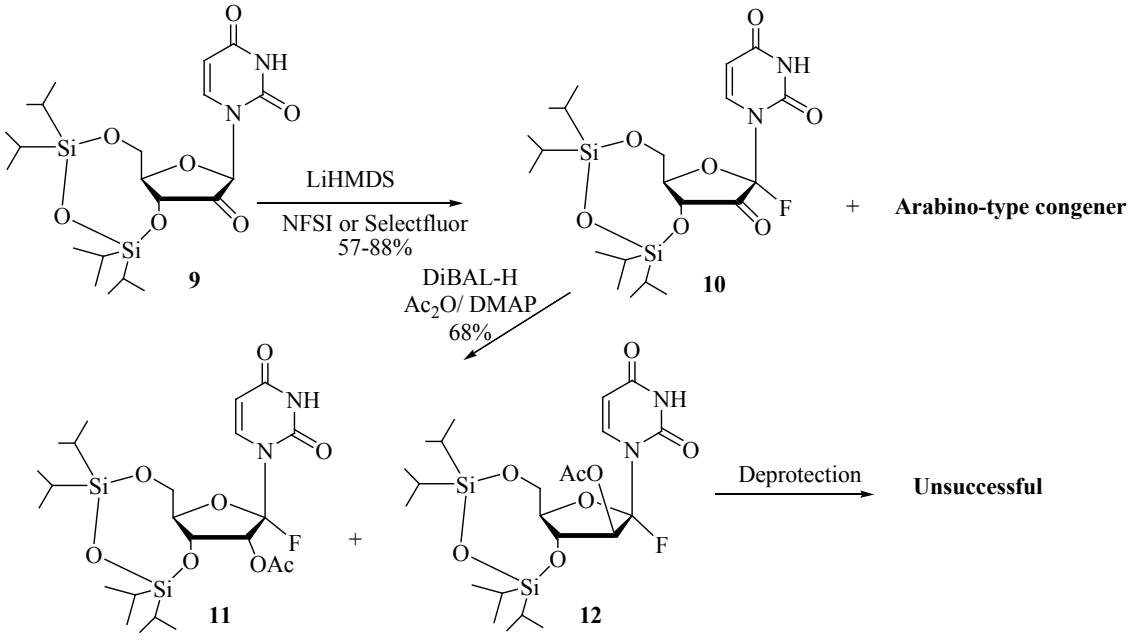
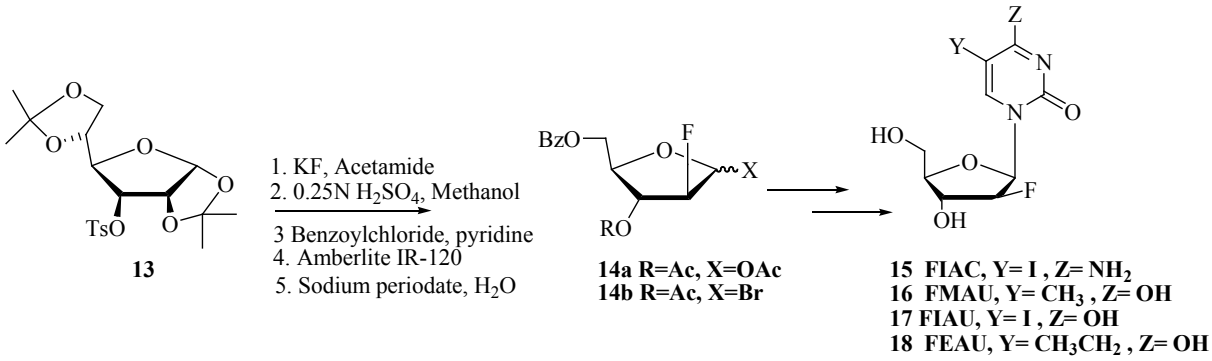


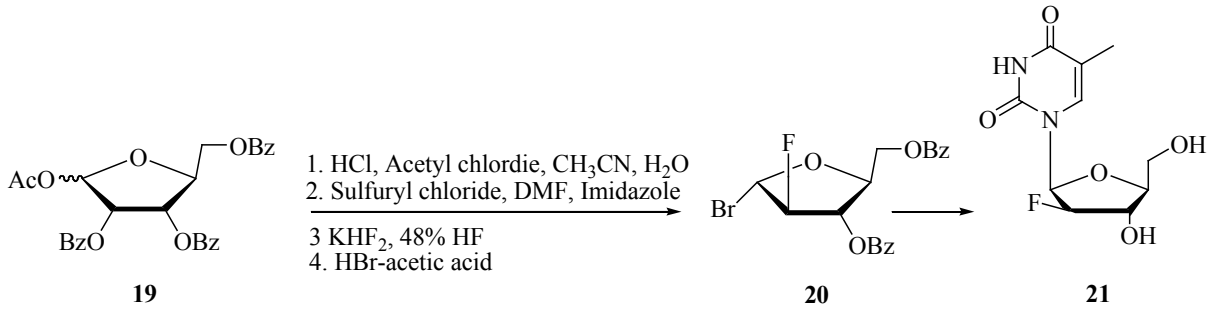
Figure 3: 5'-Fluoronucleosides.



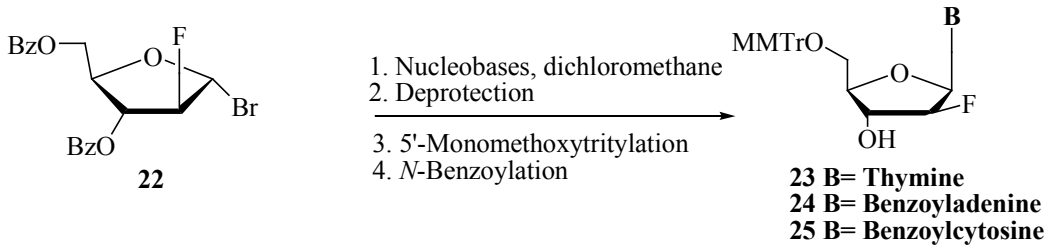
Scheme 1: Synthesis of Protected 1'-Fluoronucleosides



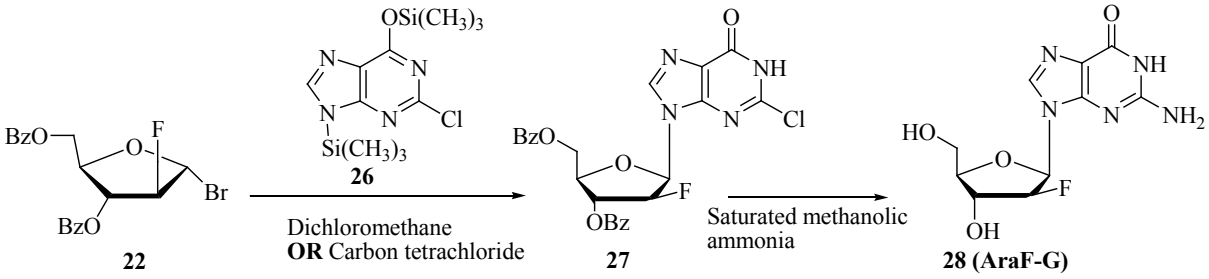
Scheme 2: Synthesis of 2'-Fluorinated Pyrimidine Nucleosides



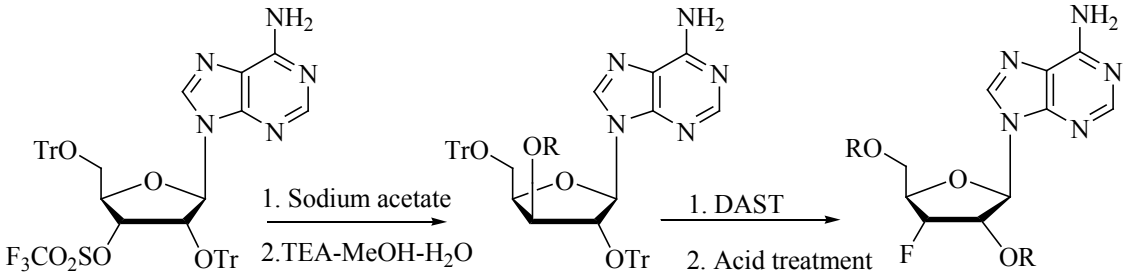
Scheme 3 : Synthesis of 1-(2-Deoxy-2-Fluoro-β-L-Arabinofuranosyl)-5-Methyluracil



Scheme 4: Synthesis of Protected AraF-Nucleosides



Scheme 5: Synthesis of AraF-G

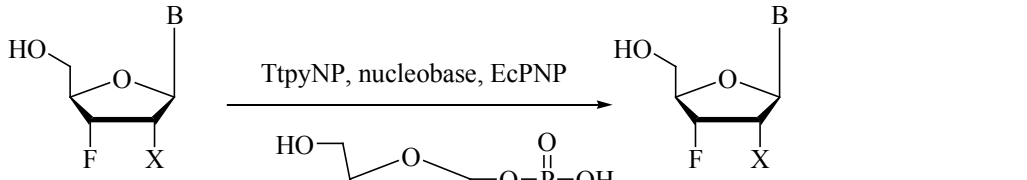


32

30 R= Ac
31 R= H

32 R= Trityl
33 R= H

Scheme 6: Synthesis of 9-(3-Deoxy-3-Fluoro-β-D-Ribofuranosyl) Adenine

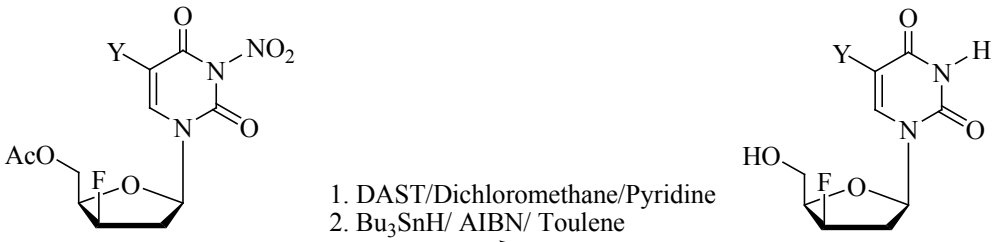


5 B=Uracil
X= OH
34 B= Thymine
X= H

X= OH or H

35a B= adenine, X= OH
35b B= 2-Aminoadenine, X= OH
36 B=Guanine, X= OH
37a B= 2-Chloroadenine, X= H
37b B= 2-Fluoroadenine, X=H

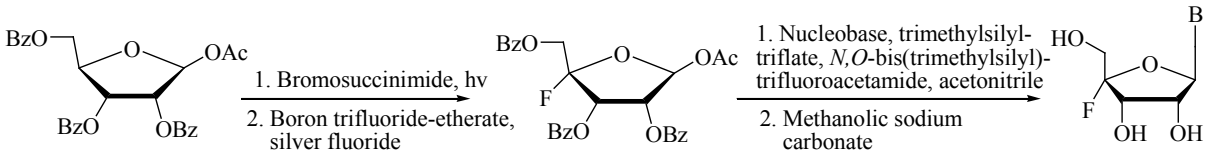
Scheme 7: Synthesis of 3'-Fluorinated Purine Nucleosides



38a Y= H
38b Y=CH_3

39a Y= H
39b Y=CH_3

Scheme 8: Synthesis of 2',3'-Dideoxy-3'-β-D-Fluoronucleosides



40

41

42 B= adenine
43 B= cytosine
44 B= hypoxanthine

Scheme 9: Synthesis of 4'-Fluorinated Nucleosides