Journal of Fluorine Chemistry 143 (2012) 11–48

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Review

Synthesis and applications of fluorinated nucleoside analogues

Hanna Wójtowicz-Rajchel *

Adam Mickiewicz University, Department of Chemistry, Grunwaldzka 6, 60-780 Poznań, Poland

ARTICLE INFO

Article history:
Received 16 April 2012
Received in revised form 20 June 2012
Accepted 27 June 2012
Available online 4 July 2012

Keywords:
Fluorinated nucleosides
Nucleoside analogues
Antiviral activity

ABSTRACT

The synthesis of fluorinated highly modified nucleoside analogues—carbanucleosides, aromatic nucleosides, acyclic nucleosides and related derivatives are reviewed.

Contents

1. Introduction

Fluorinated analogues of natural substances are mainly of interest in bioorganic chemistry since replacement of hydrogen with fluorine atoms often increases the biological activity of parent compounds. Nucleosides make a very important group of molecules, both chemically and biologically. Their primary biological role of constituents of nucleic acids has made them primary targets of antimetabolite-based therapy, where mimics of natural molecules disrupt biological processes causing death of cancer or virally infected cells. The clinical importance of human viral diseases, in particular AIDS and hepatitis caused by hepatitis viruses, generated extensive resources for the search of new antiviral agents, and as a result, a number of highly modified nucleosides, such as carbocyclic, heterosubstituted, aromatic and acyclic analogues. Fluorine containing nucleosides and their analogues have drawn special attention because of many unique properties. One of the common classical bioisosteric substitution is the incorporation of fluorine into a compound in replacement of a hydroxyl group. Fluorine is the most electronegative element which can serve as an isopolar and isosteric mimic of a hydroxyl group since the C–F bond length (1.35 Å) is close to the C–O bond length (1.43 Å). It is also the second smallest atom and closely mimics hydrogen without distortion of the geometry of the modified structure, the van der Waals radius of the fluorine (1.47 Å) is intermediate between that of hydrogen (1.2 Å) and

* Tel.: +48 61829 1304.
E-mail address: wojto@amu.edu.pl.

0022-1139/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2012.06.026

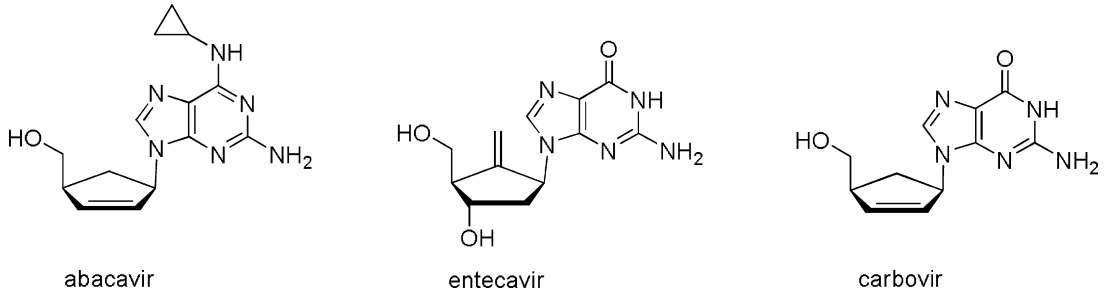


Fig. 1. Some carbocyclic nucleosides with anti-HIV activity.

oxygen (1.52 Å) [1]. Furthermore, the strength of the C–F bond exceeds that of the C–H bond which often results in increased biological and chemical stability of organofluorine compounds. It has been established that fluorine at position C-2′ of the carbohydrate moiety can provide acidic and enzymatic stabilities to the glycosidic bond by retarding oxonium ion formation and by altering the conformation of sugar moiety, respectively [2,3]. On the basis of these principals, some highly active fluorinated nucleosides have been synthesized and used in cancer and viral treatment. For example, 2′-deoxy-2′,2′-difluorocytidine (gemcitabine), a deoxycitidine analogue modified with two fluorine atoms at position 2′, has been approved as a drug against solid tumours [4]. Many aspects of the chemistry of fluorinated nucleosides have been reviewed in the last decade. Fluorine atoms can be present either on the base moiety or on sugar. The reviews generally concentrated on the synthesis of fluorinated nucleosides that contained a fluorinated glykone moiety and included the categories of 2′-, 3′-, 4′-, 5′- and 6′-fluorinated nucleosides [5–7]. Most recently Qing has comprehensively reviewed the carbohydrate-modified fluoronucleosides, substituted on the sugar part, and their thio-, aza- and carbocyclic analogues [8]. The reviews have not covered a group of fluorinated nucleosides with structural modifications of nucleobases and fluorinated acyclic nucleosides.

The intention of this review is to present the findings regarding the synthesis of highly modified fluorinated carbanucleosides, aromatic nucleosides and acyclic nucleosides. When discussing the analogues of aromatic "universal" nucleosides whose basic part has been replaced by an aromatic substituent, it seems natural to mention fluorinated analogues of deazapurine nucleosides. Similarly, acyclic analogues of nucleosides fluorinated in the pseudoglykonic part should not be discussed without a brief mention of the syntheses of fluoroalkenyl derivatives of nucleic acid derivatives which often are the synthons of the former. This review is composed of four parts covering the synthesis of fluorinated carbanucleosides, fluorinated aromatic analogues of nucleosides and deazapurine nucleosides, fluorinated acyclic nucleosides and fluoroalkenyl derivatives of nucleosides and nucleobases. It was not the intention of the paper to give a list of the fluorinated modified analogues of nucleosides known in literature, but rather to indicate general trends and direction of development in the field.

2. Carbanucleosides

Carbocyclic nucleosides are nucleoside analogues with the oxygen atom of natural nucleosides replaced by a methylene group. The isosteric replacement of the ribose oxygen with a methylene group confers cyclopentyl nucleosides a very different nature compared to the natural molecules they mimic. In fact, the C-1′ position is no longer anomeric, and the C-1′–N bond is aminic, hence more stable than the aminal functionality in natural nucleosides. This also means that glycosydation reactions, such as the popular Vorbrüggen method [9], are not applicable to the synthesis of carbocyclic nucleosides. Nucleoside analogues which are good substrates for cellular kinases but resistant to other host enzymes such as phosphorylases which cleave the glycosidic bond of natural nucleosides, are essential for the development of therapeutic agents. Because of the absence of the natural glycosidic bond, these carbanucleosides possess greater metabolic stability as they are inert towards the hydrolytic activity of the cellular phosphorylases. Many carbocyclic nucleosides have been so far identified to exhibit antiviral and antitumour activities [10,11]. Abacavir has been used as an anti-HIV agent [12], entecavir, a carbocyclic nucleoside with an exocyclic double bond and carbovir are endowed with a potent anti-HIV activity [13–15] (Fig. 1).

Carbanucleosides can be classified according to the size of the ring as cyclopropane, cyclobutane, cyclopentane and cyclohexane derivatives.

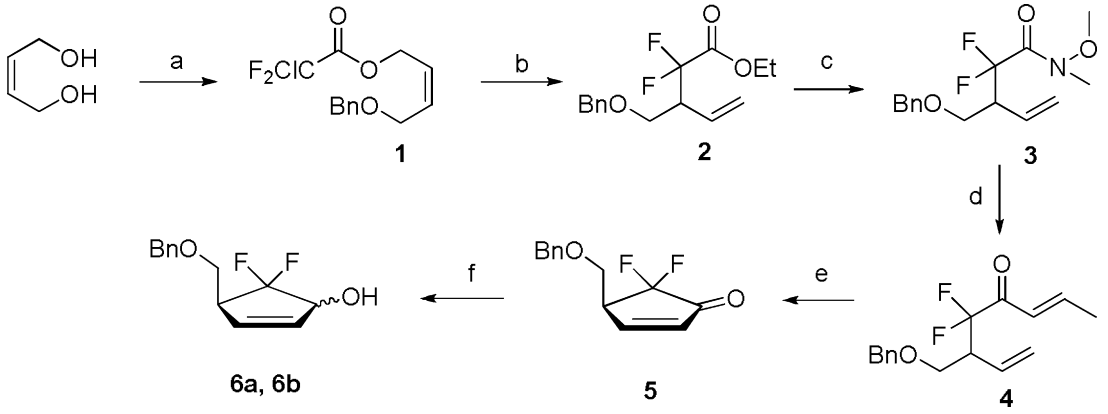
2.1. Fluorinated cyclopentyl nucleosides

The *gem*-difluoromethylene CF_2 group has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen [16,17]. Since then, the CF_2 group was used extensively to modify nucleoside analogues.

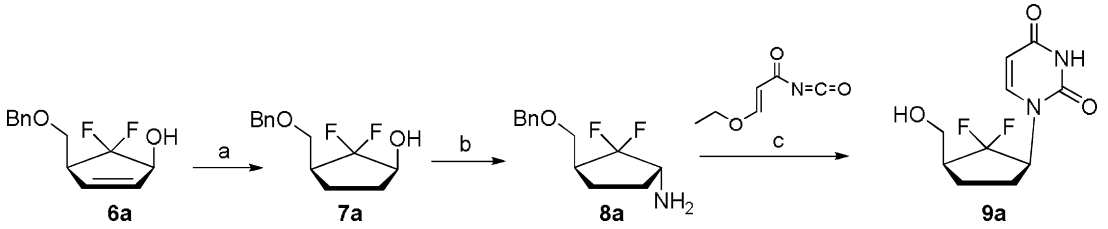
Thus Qing and coworkers [18] have synthesised from (Z)-but-2-ene-1,4-diol in 14 steps, 2′,3′-dideoxy-6′,6′-difluorouracils **9a** and **9b**, a novel series of *gem*-difluoromethylenated carbocyclic nucleosides. A notable step was the construction of the carbocyclic ring *via* ring-closing metathesis (RCM) and the incorporation of *gem*-difluoromethylene group by way of silicon-induced Reformatskii–Claisen reaction of chlorodifluoroacetic ester **1** (Scheme 1). The final alcohols **6a** and **6b** can be separated easily by column chromatography. Hydrogenation of **6a** with the catalyst of Pd/C gave compound **7a**. Treatment of alcohol **7a** with trifluoromethanesulphonic anhydride and pyridine followed by substitution reaction with sodium azide in DMF gave the azide compound which was directly reduced by hydrogenation to give cyclic amine **8a**. The construction of pyrimidine followed by the known procedure gave the target molecule **9a**. With the same synthetic route, isomer **9b** was prepared from **6b** (Scheme 2).

The synthesis of the racemic *gem*-difluoromethylated carbocyclic nucleoside **12** was described by Borthwick's group (Scheme 3) [19,20]. The carbocyclic 2′,2′-difluorothymidine analogue **12** was obtained from the protected difluoro amino diol **10** and the key steps involved the oxidation of alcohol and the subsequent *gem*-difluoromethylation with DAST. After deprotection with tetrabutylammonium fluoride (TBAF), thymine base was installed *via* treatment of the compound **11** with 3-ethoxyacryloyl isocyanate in the presence of DBU followed by sulphuric acid.

Using a stereoselective Reformastskii–Claisen rearrangement, RCM and palladium-catalyzed allylic alkylation as the key steps, Qing and co-workers successfully accomplished the synthesis



Scheme 1. Reagents: (a) i. NaH, $PhCH_2Br$, DMF, ii. $ClCF_2CO_2H$, H_2SO_4, toluene, (b) i. TMSCl, zinc dust, CH_3CN, ii. H_2SO_4, C_2H_5OH, (c) N,O-dimethylhydroxylamine, $AlMe_3$, toluene, (d) i. CH_2CHCH_2MgBr, THF, ii. Et_3N, (e) Grubb's catalyst, toluene and (f) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, CH_3OH.



Scheme 2. Reagents: (a) H_2, Pd black, benzene, (b) i. Tf_2O, CH_2Cl_2, ii. NaN_3, DMF, iii. H_2, Pd black, benzene and (c) i. DMF, ii. 2 N H_2SO_4, iii. H_2, Pd/C.

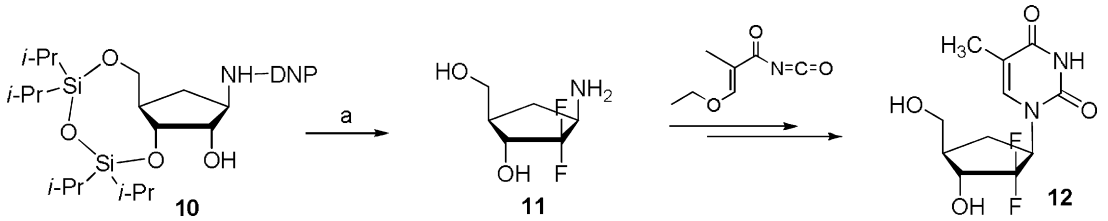
of 3′,3′-difluoro-2′-hydroxymethyl-4′,5′-unsaturated carbocyclic nucleosides from the ester **13** [21]. The Reformatskii–Claisen reaction of **13** and subsequent esterification gave the *gem*-difluorinated ester **14**. The ester was converted into the separable Weinreb amides and preparation of the RCM precursor **15** was completed *via* treatment with allylmagnesium chloride followed by Luche reduction. Alcohol **15** in RCM reaction gave the separable cyclic alcohols **16** and **17**. Reaction of **17** with methyl chloroformate produced the corresponding allylic carbonate, which reacted with 3-benzoylthymine under the catalysis of $Pd(PPh_3)_4$ to yield the γ-substituted compound **18**. The target nucleoside **19** was obtained *via* convenient removal of the protecting groups, oxidation with $NaIO_4$ and subsequent reduction with $NaBH_4$ (Scheme 4).

Schneller and coworkers have realized the synthesis of 4′,4′-difluoro analogue **26** of 5′-noraristeromycin (Scheme 5) [22]. Their synthesis commenced with treatment of acetate **20** with monochloroacetic acid under Mitsunobu conditions, and the chloroacetate ester **21** was provided. After selective cleavage of the ester moiety in **21** with thiourea/$NaHCO_3$, the resultant hydroxyester **22** was subjected to a second Mitsunobu reaction with 6-chloropurine to give the acetate **23**. Dihydroxylation of the compound **23** and the subsequent isopropylidination afforded the intermediate, which, after deacetylation with KCN/MeCN/H_2O to form **24**, was further oxidized with PCC to furnish ketone **25**. DAST-mediated *gem*-difluoromethylation followed by ammonolysis and deprotection provided the desired 4′,4′-difluoro nucleoside analogue **26**.

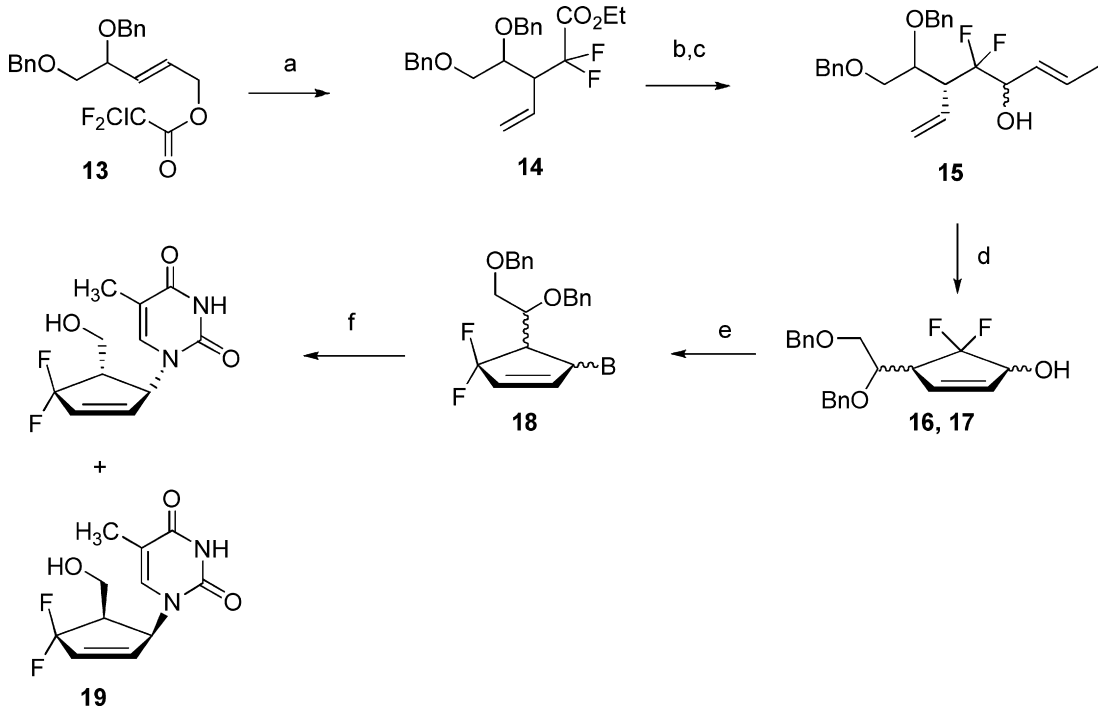
They have also developed an entry to the 3′,3′-difluoro carbocyclic nucleoside analogue **29**, by using a similar method to introduce *gem*-difluoromethyl group, *i.e.*, oxidation of the secondary hydroxyl group to get intermediate **27**, followed by fluorination with DAST to give the key compound **29** (Scheme 6) [23].

Prisbe and coworkers [24] have synthesized and biologically evaluated 6′-fluorinated aristeromycin **33** and **36** (Scheme 7). Aristeromycin (Fig. 2), the carbocyclic analogue of adenosine exhibits a number of interesting biological properties including inhibition of AMP synthesis in mammalian cells. The synthesis started from the epoxy diol **30**. After functionalized **31** was prepared using their reported procedure, the fluorine atom was introduced *via* a nucleophilic substitution reaction to give compound **32**. Fluorinated derivative of β-fluoroaristeromycin **33** was delivered in several steps, which involved the reduction of the azide **32**, elaboration of the 9-adeninyl substituent and deprotection. The monotritylation of epoxy diol **30**, reversing the configuration of the C-6 hydroxyl group, was realized *via* a nucleophilic substitution reaction to get epimeric alcohol **34**. Trifluoromethanesulphonation of compound **34** and subsequent reaction with TBAF furnished the α-fluoro epoxide **35**. The compound was converted into 6′-α-fluoroderivative **36** through treatment with adenine in the presence of K_2CO_3 followed by deprotection.

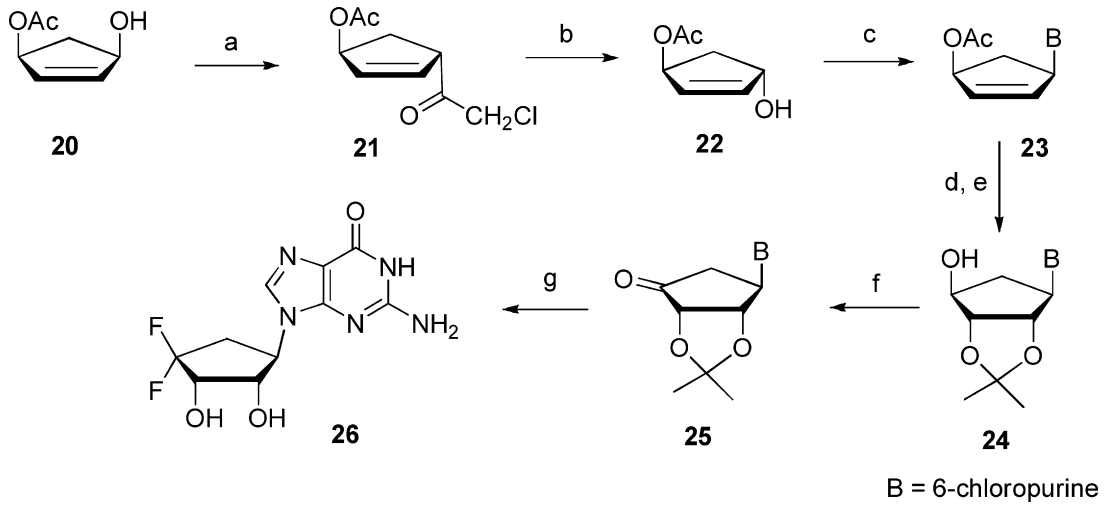
Schmeller and Yin have reported the chiral synthesis of 6′-fluorocarbocyclic nucleoside **33** [25] as a representative of the C-6′



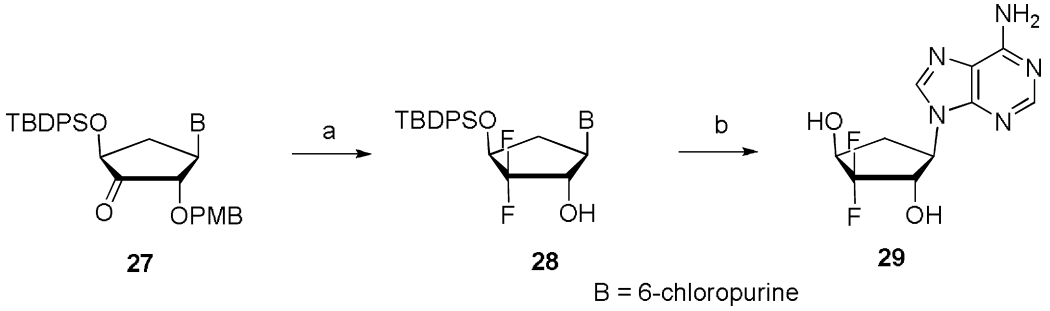
Scheme 3. Reagents: (a) i. $(CF_3CO)_2O$, DMSO, ii. DAST, iii. TBAF, iv. Amberlite IR-400.



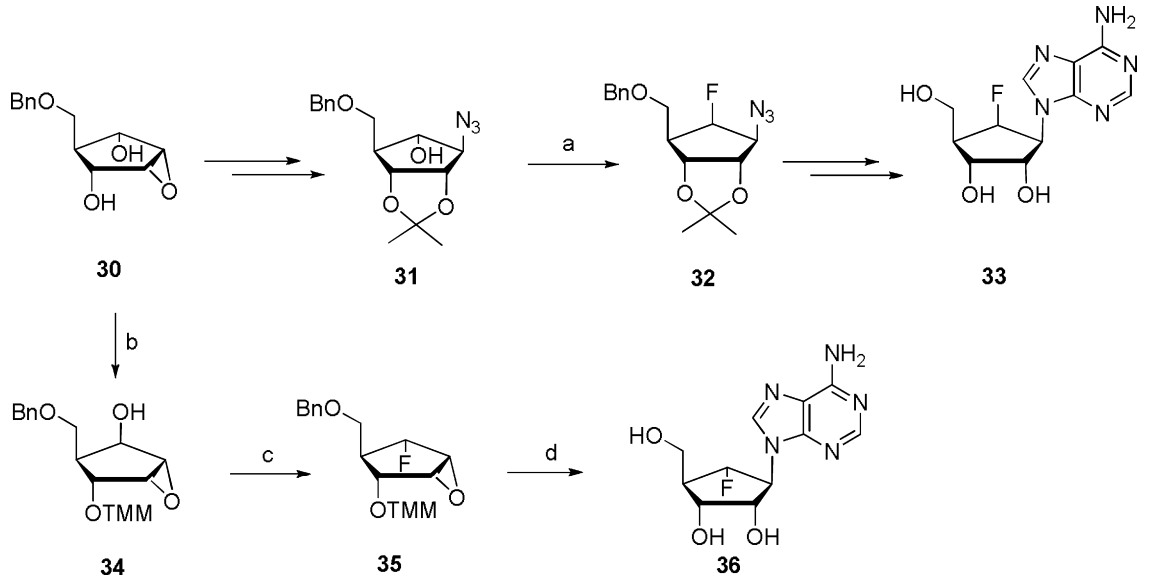
Scheme 4. Reagents: (a) i. TMSCl, Zn dust, CH_3CN, ii. H_2SO_4, C_3H_5OH, (b) $HNCH_3OCH_3{\cdot}HCl$, *n*-BuLi, THF, (c) i. allylmagnesium chloride, THF, ii. Et_3N, iii. $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH, (d) Grubb's catalyst, toluene, (e) i. CH_3OCOCl, pyridine, ii. 3-Bz-thymine, $Pd(PPh_3)_4$, PPh_3, THF and (f) i. NH_3, CH_3OH, ii. BCl_3, CH_2Cl_2, $NaIO_4$, CH_3OH, iv. $NaBH_4$.



Scheme 5. Reagents: (a) PPh_3, DIAD, $ClCH_2CO_2H$, (b) thiourea, $NaHCO_3$, (c) PPh_3, DIAD, 6-chloropurine, (d) i. OsO_4, NMMO, ii. DMP, (e) KCN, CH_3OH, H_2O, (f) PCC, CH_2Cl_2 and (g) i. DAST, CH_2Cl_2, ii. NH_3, CH_3OH.



Scheme 6. Reagents: (a) DAST, CH_2Cl_2 and (b) NH_4F, CH_3OH.



Scheme 7. Reagents: (a) i. Tf_2O, pyridine, ii. TASF, (b) i. MMTrCl, pyridine, ii. Tf_2O, DTBMP, iii. BzLi, DMF, iv. NH_3 CH_3OH, (c) i. Tf_2O, DTBMP, ii. TBAF, THF and (d) i. adenine, K_2CO_3, ii. HCO_2H, CH_3OH, iii. $Pd(OH)_2$, cyclohexane.

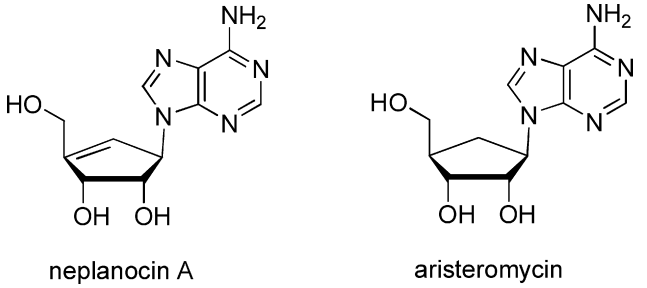


Fig. 2. Carbocyclic analogues of adenosine.

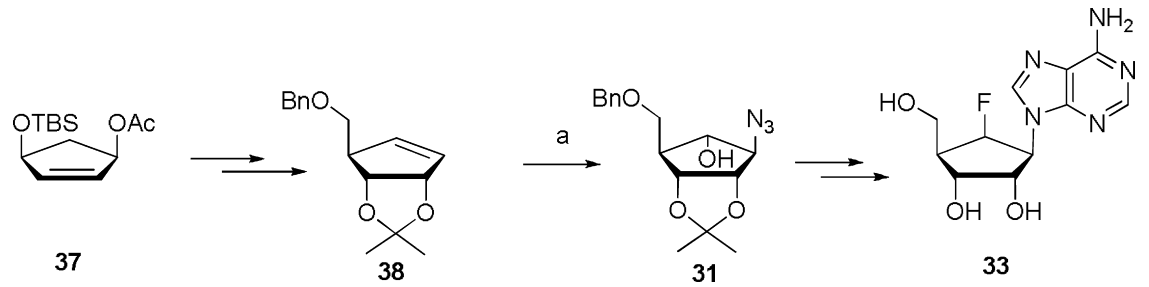
substituted carbocyclic series that has shown promising potential as an antiviral agent. Their synthesis was built upon compound **37**, which was converted into cyclopentene **38** (Scheme 8). The sequence of deisopropylidenation, epoxidation, sodium azide ring opening and re-isopropylidenation gave azide **31** and its isomer. Using the same strategy as that described by Prisbe [24] the target nucleoside **33** was obtained.

Jeong's group have synthesized fluoroneplanocin A **43** [26] and found that it exhibited more potent SAH inhibitory activity than neplanocin A. The parent neplanocin A, the carbocyclic cyclopentenyl analogue of adenosine, is a natural antibiotic that inhibits S-adenosylhomocysteine hydrolase (SAH) (Fig. 2) [27]. They started from the cyclopentenone derivative **39**, which was converted into its iodide **40** through iodination, followed by Luche reduction and deprotection (Scheme 9). The treatment of **40** with Selectfluor/*n*-BuLi followed by TBAF-mediated desilylation and mesylation gave compound **41** which was condensed with the adenine anion to generate the protected nucleoside **42**. Deprotection of **42** yielded the target product **43**.

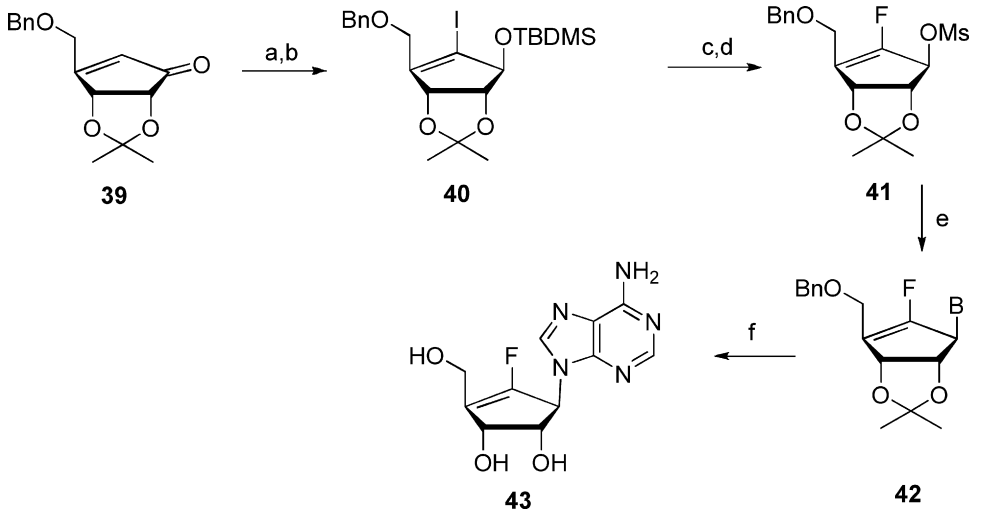
α-Fluorination of the cyclopentanone derivative with Selectfluor was another way to synthesize 6′-fluorocarbocyclic nucleosides. Samuelsson and coworkers [28] described an asymmetric synthesis of 6′-α- and 6′-β-monofluorinated carbanucleosides (Scheme 10). Thus, silylenol ether **45** which was prepared from cyclopentanone **44** was treated with Selecfluor to give inseparable mixture of the fluoroketones **46**. Selective reduction of the ketone gave two diastereomeric alcohols, the key intermediate **47** for 6′-fluoronucleosides **48**.

Most recently, in 2011 Qing and coworkers obtained 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides **55** and **56** [29]. The design of unsaturated 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides was based on the fact that 2′,3′-dideoxynucleosides are analogues of the highly bioactive carbovir and abacavir. The synthesis of target molecules began by preparation of allyl bromofluoroacetate **50**. Treatment of allylic alcohol **49** with bromofluoroacetyl chloride afforded ester **50**. Then the silicon-induced Reformatskii–Claisen reaction of compound **50** followed by esterification provided the monofluorinated esters as four diastereoisomers and the major diastereoisomer **51** was separated by flash chromatography (Scheme 11).

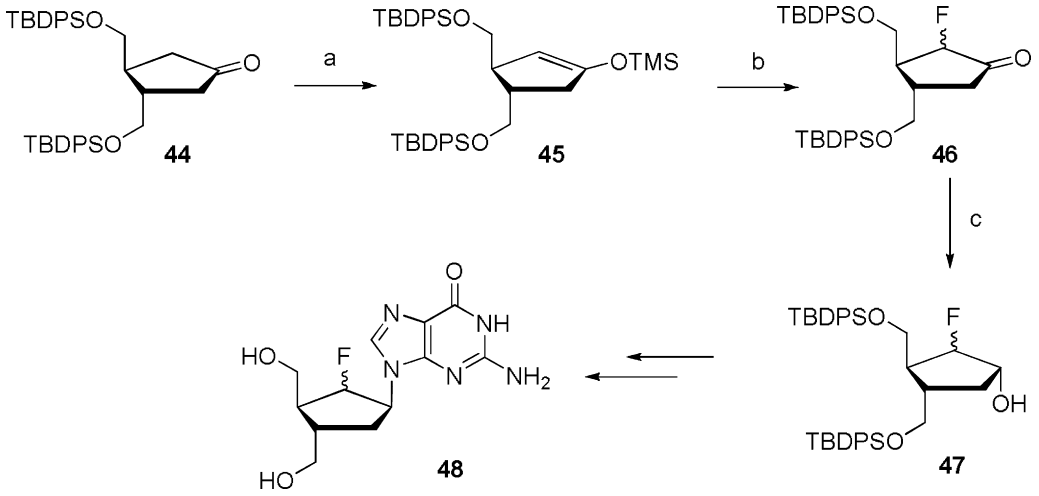
Ester **51** was transformed to amide and the allylation with allylmagnesium chloride followed by triethylamine-induced double bond isomerization gave the α,β-unsaturated ketone **52**.



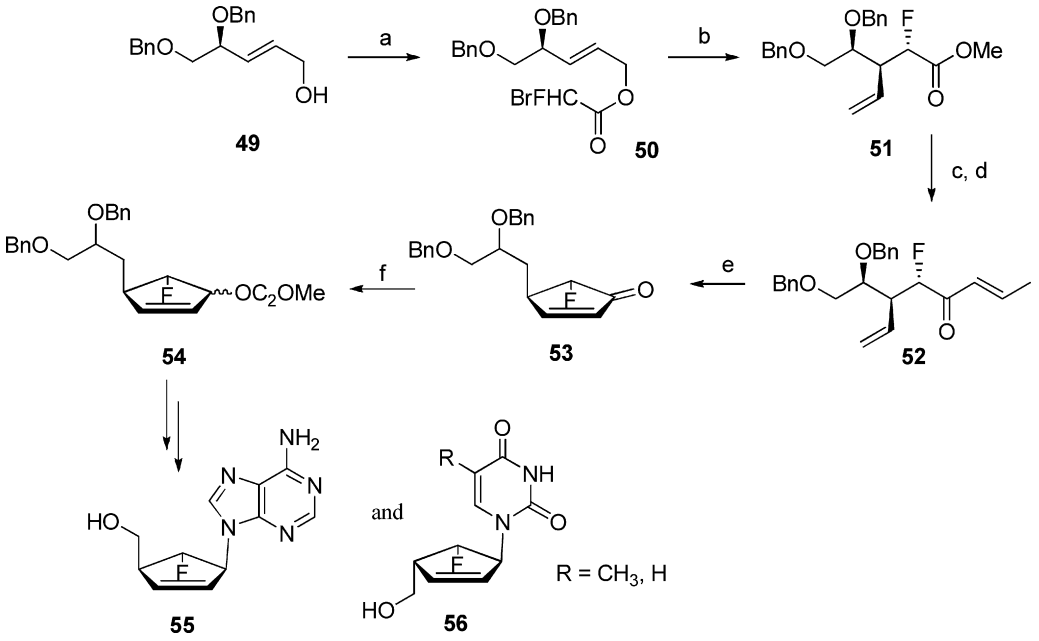
Scheme 8. Reagents: (a) i. HCl, CH_3OH, ii. *m*-CPBA, iii. NaN_3, DMF, iv. DMP, PTSA.



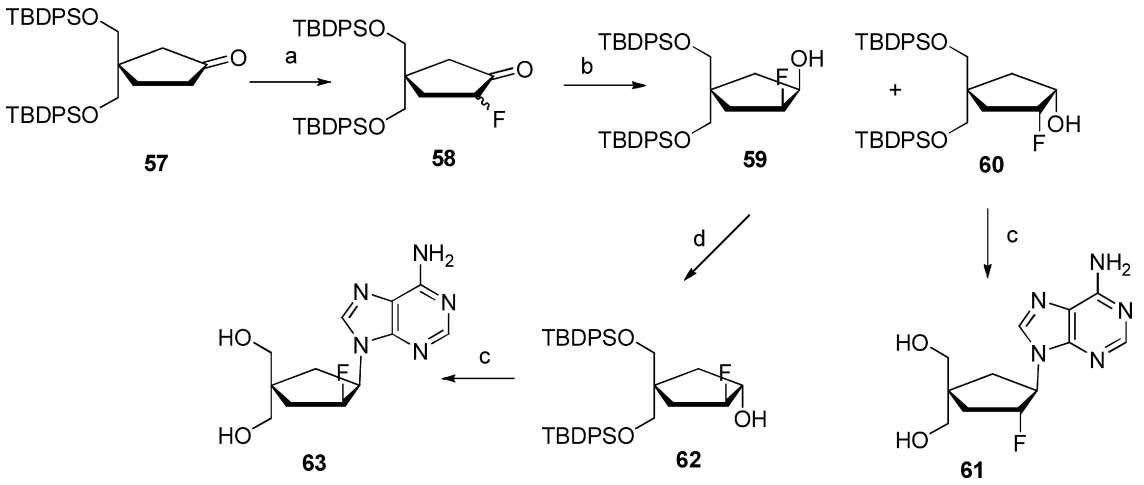
Scheme 9. Reagents: (a) i. I_2, pyridine, ii. $NaBH_4$, $CeCl_3$, (b) TBDMSCl, imidazole, (c) i. Selectfluor, *n*-BuLi, ii. TBAF, THF, (d) MsCl, pyridine, (e) adenine, K_2CO_3, 18-crown-6, DMF and (f) i. BBr_3, CH_2Cl_2, ii. Ac_2O, pyridine, iii. NH_3, CH_3OH.



Scheme 10. Reagents: (a) TMSOTf, Et_3N, toluene, (b) Selectfluor, DMF and (c) LS-selectride, THF.



Scheme 11. Reagents: (a) $CHFBrCOCl$, pyridine, CH_2Cl_2, (b) i. Zn, TMSCl, CH_3CN, ii. $SOCl_2$, CH_3OH, (c) $CH_3NHOCH_3{\cdot}HCl$, $AlMe_3$, CH_2Cl_2, (d) i. allylmagnesium chloride, ii. Et_3N, (e) Grubb's II catalyst, toluene and (f) i. $NaBH_4$, $CeCl_3{\cdot}7H_2O$, ii. $ClCO_2CH_3$.



Scheme 12. Reagents: (a) i. TMSOTf, Et_3N, ii. Selectfluor, (b) LS-selectride, THF, (c) i. 6-chloropurine, PPh_3, DIAD, THF, ii. NH_3 CH_3OH, dioxane, iii. TBAF, THF and (d) i. BzOH, PPh_3-DIAD, ii. CH_3ONa, CH_3OH.

RCM process of diene **52** with Grubbs-II catalyst provided the desired product **53**. The reduction of compound **53** afforded alcohols which were converted to allyl carbonates **54**. The Mitsunobu reaction was used for introduction of bases giving successful access to nucleosides **55** and **56**.

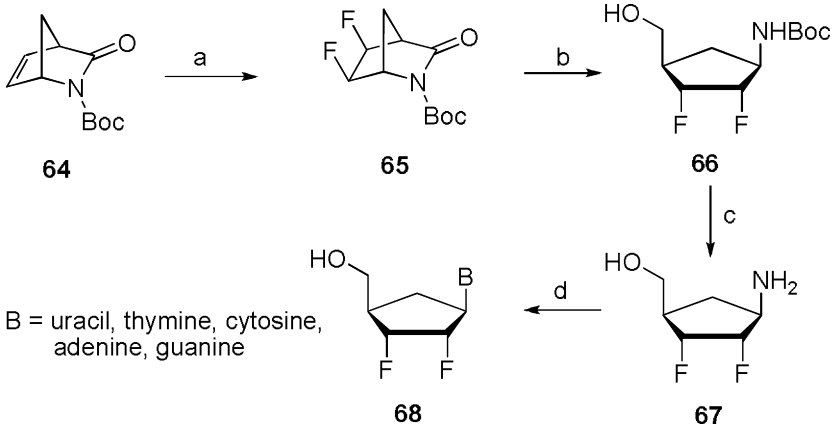
The carbocyclic 2′,3′-dideoxy-2′-fluoro-3′-C-hydroxymethylpurine nucleosides **61** and **63,** designed as potential inhibitors of HIV and HSV, have been synthesized by Samuelsson and coworkers [28,30]. Their synthesis started from the cyclopentanone derivative **57**, which was treated with TMSOTf/Et_3N followed by Selectfluor to give the fluoroketones **58** (Scheme 12). Stereoselective reduction gave two alcohols **59** and **60**, which were separated by column chromatography. The configuration of the hydroxyl group at C-1′ in **59** was inverted using a Mitsunobu reaction *via* treatment with benzoic acid, followed by debenzoylation to give compound **62**. The desired purine nucleosides **61** and **63** were obtained from **60** and **62**, respectively, by means of coupling with 6-chloropurine using the Mitsunobu procedure followed by treatment with methanolic ammonia and deprotection.

Toyota and coworkers have found that the addition of molecular fluorine to the bicyclo[2.2.1]hept-2-ene derivative **64** afforded the corresponding *exo* adduct **65**, from which a series of 2′,3′-difluorinated carbocyclic nucleosides **68** were synthesized (Scheme 13) [31]. Reductive amide-bond cleavage of **65** using $NaBH_4$ first gave the alcohol **66** and after treatment with TFA the aminoalcohol **67**. Installation of pyrimidine and purine bases provided the target carbocyclic nucleosides **68**.

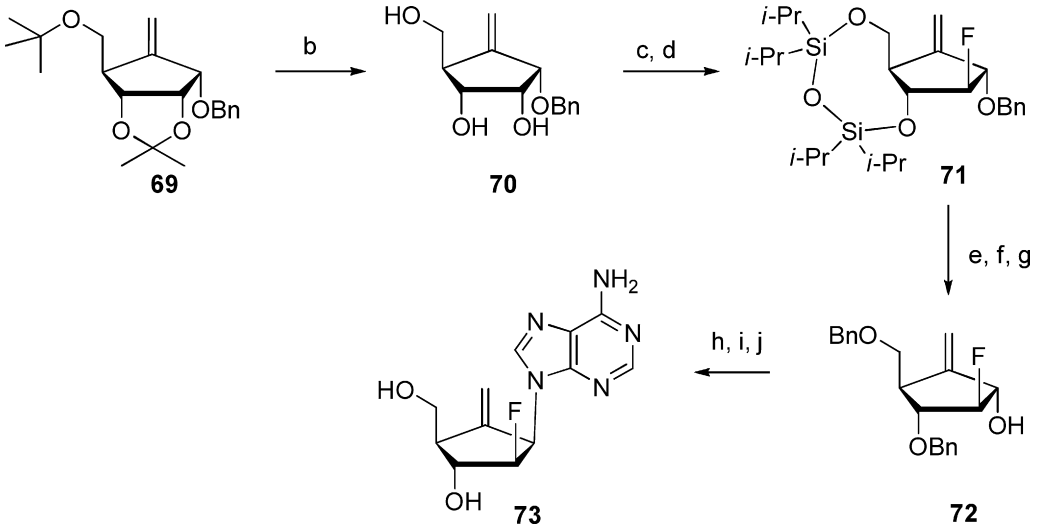
In 2011, Chu and coworkers synthesized a novel 2′-fluoro-6′-methylene-carbocyclic adenosine **73** [32]. The target nucleoside demonstrated significant anti-HBV activity against both the wild-type as well as the major nucleoside-resistant HBV mutants.

The synthesis of nucleoside **73** commenced with compound **72** as the key intermediate (Scheme 14). In substrate **69** the allylic hydroxyl group was protected with a benzyl group and subsequent deprotection of the acetonide and the *t*-butyl group of compound **69** gave **70**. The hydroxyl groups of **70** were selectively protected with 1,3-dichloro-1,1,2,2-tetraisopropyl disilazane to give alcohol and the transformation of the 2-β-hydroxyl group to 2-α-fluoro was accomplished with DAST to give compound **71**. The silyl group was removed by using TBAF to a diol, which was re-protected by benzoyl chloride to give the fully protected intermediate which was then treated with BCl_3 to obtain the key intermediate **72**. The N,N-diboc protected adenine was condensed with **72** and after deprotection of the Boc groups with TFA compound **73** was afforded.

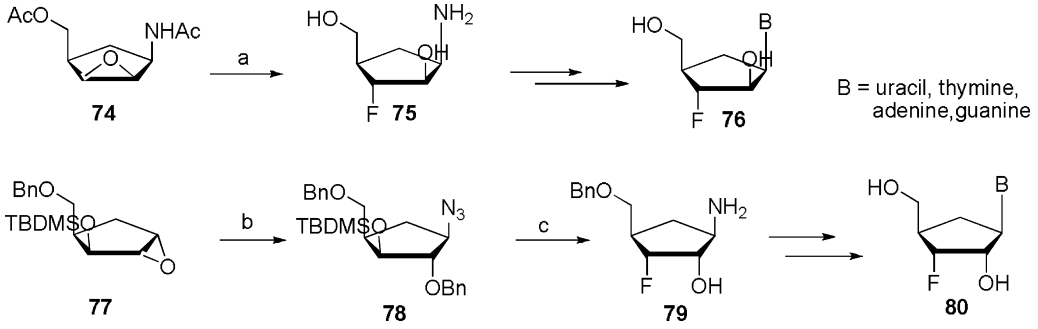
A series of carbocyclic analogues of nucleosides substituted at position 3′ with a fluorine atom have been synthesized by Morizwa group [33]. Their synthetic strategy featured the preparation of two key intermediates **75** and **78** by means of the ring opening of epoxides **74** and **77** with HF/pyridine and NaN_3 (Scheme 15). Fluorination of compound **78** with PST gave the fluorinated azide, which was hydrogenated with Pd/C as a catalyst to yield fluoro amino diol **79**. The racemic carbocyclic analogues **76** of 3′-deoxy-3′-α-fluoro-ribo-furanosides and the carbocyclic analogues **80** of



Scheme 13. Reagents and conditions: (a) F_2, (b) $NaBH_4$, (c) CF_3CO_2H and (d) base installation.



Scheme 14. Reagents: (a) NaH, BnBr, DMF, (b) CF_3CO_2H/H_2O, (c) $TIDPSCl_2$, imidazole, DMF, (d) DAST, CH_2Cl_2, (e) TBAF/AcOH, THF, (f) BzCl, pyridine, (g) BCl_3, CH_2Cl_2, (h) *N*,*N*-dibocprotected adenine, DIAD, Ph_3P, THF, (i). CF_3CO_2H, CH_2Cl_2 and (j) DIBAL-H, CH_2Cl_2.



Scheme 15. Reagents: (a) i. HF, pyridine, ii. diluted HCl, (b) i. NaN_3. ii. BnBr, NaH and (c) i. TBAF, ii. TMSCl, iii. PST, iv. H_2, Pd/C.

3′-deoxy-3′-α-fluoro-arabino-furanosides were provided *via* installation of the nucleic acids bases from the amine groups of the fluoro amino diols **75** and **79** using the general reaction procedures.

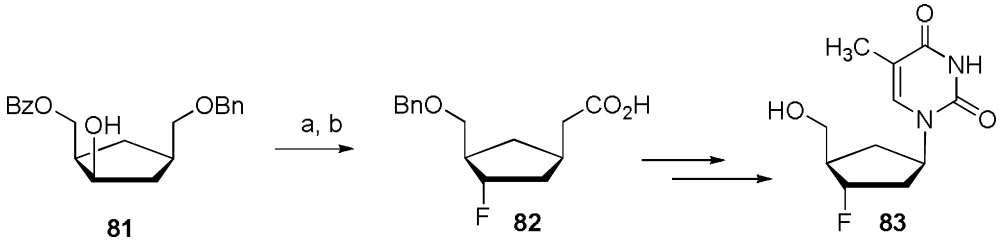
The carbocyclic 2′,3′-deoxy-3′-α-fluorothymidine **83** was also successfully accessed by the Griengl group *via* DAST-mediated fluorination of compound **81** and installation of a thymine base from the carboxyl group (amino group) of compound **82** as the key steps (Scheme 16) [34].

Schneller et al. accomplished the synthesis of the both carbocyclic 3′-deoxy-3′-β-fluoroadenosine **86** and the carbocyclic 3′-deoxy-3′-α-fluoroadenosine **89** [23].

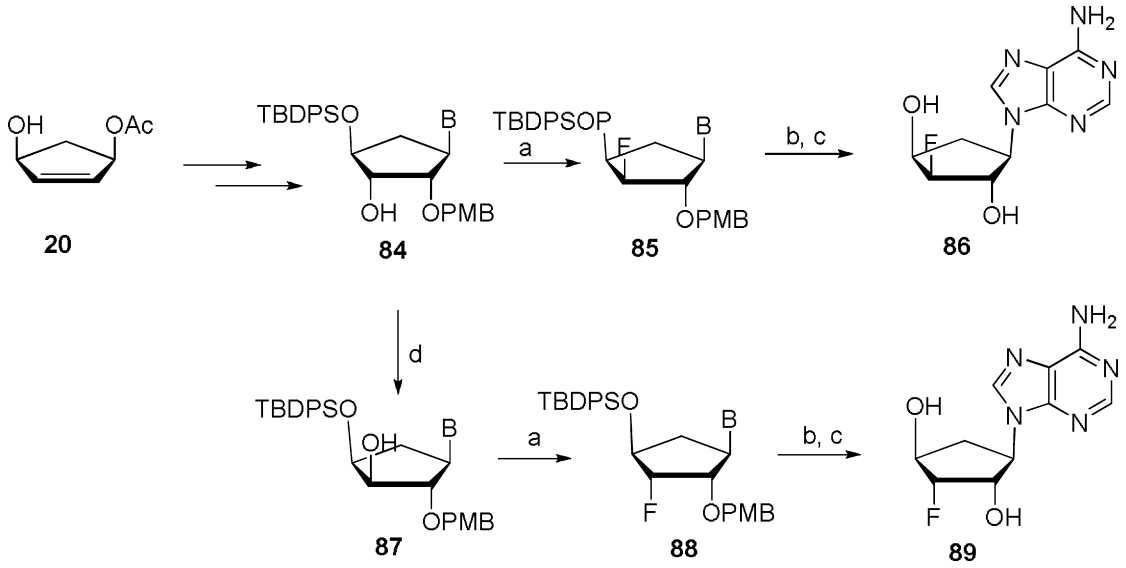
The key synthetic steps included the preparation of alcohol **84** from compound **20** *via* the introduction of 6-chloropurine base using a coupling reaction and the subsequent reactions (Scheme 17). Fluorination of compound **84** with DAST yielded the fluorinated derivative **85**, which was treated with CAN and subjected to ammonolysis and desilylation to generate the desired carbocyclic 3′-deoxy-3′-β-fluoroadenosine **86**. After inversion of the C-4′ hydroxyl group in the compound **84** *via* a Mitsunobu reaction, the isomeric carbocyclic nucleoside **89** was also prepared by means of a similar route *via* intermediates **87** and **88**.

Naturally occurred nucleocidin, 4′-α-fluoro-5′-O-sulphamoyl adenosine (Fig. 3), was first isolated as an anti-trypanosome antibiotic from *Streptomyces calvus* [35]. This nucleoside antibiotic in which fluorine is covalently bound to the C-4′ of adenosine through a C–F bond, has been a target for organic synthesis in past decades.

Considering the fact that nucleocidin analogues are potent inhibitors of protein biosynthesis Chu's group have stereoselectively synthesized the carbocyclic α-4′-fluoro-2′,3′-dideoxyadenosine **94** (Scheme 18) [36]. The key intermediate, (*E*)-alkene **91**, was prepared starting from D-glyceraldehyde **90**. After hydrogenolysis of **91** followed by mesylation of the resulting alcohol, the generated mesylate was treated with NaH to yield the enolate intermediate, which simultaneously cyclized to afford esters **92**. Hydrolysis with NaOH furnished the corresponding acids, which were subjected to oxidative iododecarboxylation followed by hydrolysis to give alcohol **93**. Coupling of **93** with 6-chloropurine



Scheme 16. Reagents: (a) DAST and (b) i. BBr_3, ii. PDC, iii. oxidation.



Scheme 17. Reagents: (a) DAST, (b) CAN, (c) i. NH_3, CH_3OH, ii. TBAF and (d) i. PPh_3, DIAD, $ClCH_2CO_2H$, ii. NH_3, CH_3OH.

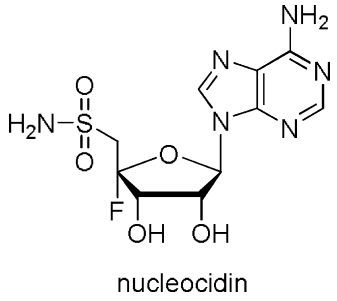


Fig. 3. Naturally occurred nucleocidin, 4′-α-fluoro-5′-O-sulphamoyl adenosine.

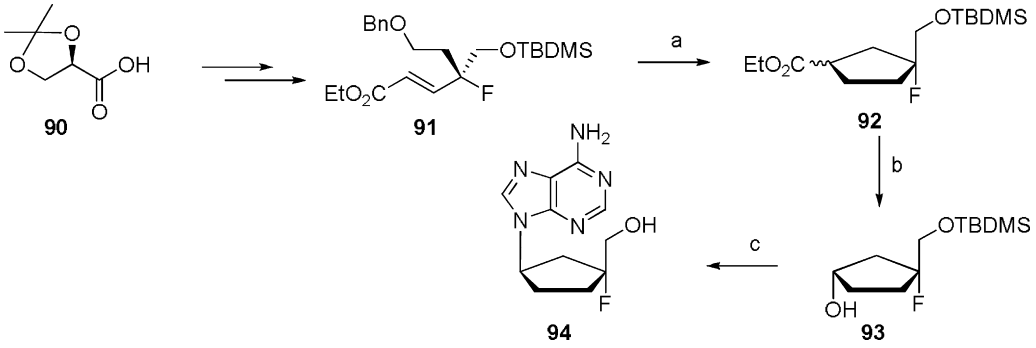
under Mitsunobu conditions followed by ammonolysis and deprotection provided the target nucleoside **94**.

Because of low yield of L-isomer synthesis, Chu's group have decided to develop a more efficient method for the synthesis of D-isomers, in which the RCM reaction of 1,6-diene allowed a more facile synthesis of D-enantiomer. They developed an efficient general route to D-4′-fluoro-2′,3′-dideoxynucleosides **99**, starting from (*E*)-allylic alcohol **95** (Scheme 19) [37]. Alcohol **95,** was oxidized by PCC, and the resulting aldehyde was subjected to carbonyl addition by vinylmagnesium bromide to result in a diastereomeric mixture of 1,6-dienes **96** which further underwent an RCM reaction to afford **97** and were converted into the mixture of α- and β- cyclopentanols **98** through hydrogenation. β-Alcohol **98** could be converted into α-epimer by Mitsunobu reaction followed by $LiAlH_4$ reduction. The α-epimer of **98** was condensed with various protected purine or pyrimidine bases followed by ammonolysis and deprotection to give the desired nucleosides **99**.

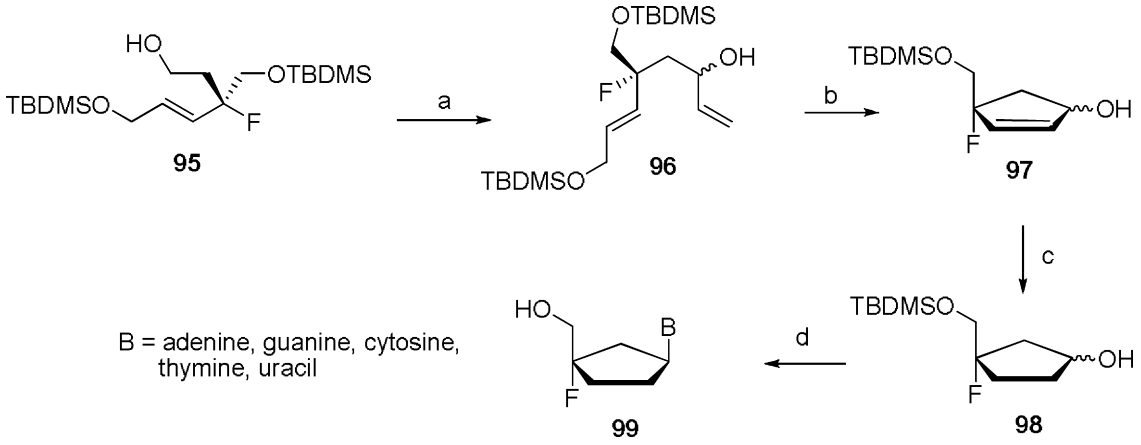
Borthwick and coworkers have accomplished the synthesis of 4′-fluorocarbocyclic-2′-deoxyguanosine commencing with aristeromycin and showed that this nucleoside revealed good activities against HSV-1 and HSV-2 [38]. The Samuelsson group have completed the synthesis of its analogue, 4′-fluorocarbocyclic-2′,3′-dideoxy-3′α-hydroxymethyl guanosine **105** [39]. In their synthesis (Scheme 20), cyclopentanol **104** was prepared from the enantiomerically pure (3S,4S)-bis(hydroxylmethyl)cyclopentanone ethylene glycol ketal **100** *via* a number of key steps involving stereospecific reduction of the keto function of compound **101** and dihydroxylation of the C-4 methylene of **102**. After protection of the primary hydroxyl group in compound **103**, replacement of the C-4 hydroxyl group with fluorine using Deoxo-Fluor and subsequent detritylation gave compound **104**. The desired nucleoside **105** was afforded by coupling of alcohol **104** with 2-amino-6-chloropurine using a Mitsunobu procedure followed by the treatment with formic acid, ammonium hydroxide and hydrogenation with Pd/H_2. Compound **105** was evaluated as potential antiviral agent for anti HSV-1 activity.

2.2. Fluorinated cyclobutyl nucleosides

Oxetanocin A (compound **A**) is the first example of a natural four membered ring nucleoside. This compound has stimulated a



Scheme 18. Reagents: (a) i. H_2, Pd/C, ii. MsCl, pyridine, iii. NaH, THF, (b) i. NaOH, C_2H_5OH–H_2O, ii. $Pb(OAc)_4$, CCl_4, I_2, iii. $NaHCO_3$, H_2O-HMPA and (c) i. 6-chloropurine, PPh_3, DEAD, ii. NH_3, CH_3OH, iii. TBAF, THF.



Scheme 19. Reagents and conditions: (a) i. PCC, CH_2Cl_2, ii. vinylmagnesium bromide, THF, (b) Grubb's catalyst, CH_2Cl_2, (c) H_2, Pd/C, cyclohexane and (d) i. DEAD, PPh_3, nucleobase or protected 6-chloropurine, ii. base transformation and deprotection.

great synthetic effort since its discovery by Shimada and co-workers in 1986 [40]. In particular, the discovery in 1990 [41], that carbocyclic analogues of oxetanocin A, compounds **B** and **C**, exhibit more potent antiherpes activities than **A**, as well as anti-HIV activity, led numerous groups to investigate original synthesis of carbocyclic oxetanocin and related substances (Fig. 4).

In view of the potent antiviral activity of the naturally occurring oxetane nucleoside oxetanocin A, Fleet and co-workers in 1991 were the first to accomplish the synthesis of fluorinated oxetanocin **109** [42]. Their synthesis was performed through DAST-mediated fluorination of trityl protected alcohol **106** followed by conversion of the resultant fluorinated compound **107** into the chlorinated product **108** (Scheme 21). The reaction of compound **108** with adenine and subsequent removal of the trityl group with TFA provided the target nucleoside **109** and its α anomer **110**.

Two years later, 2′-β-fluoro cyclobutane nucleoside analogue **114** was obtained by the introduction of a fluorine atom adjacent

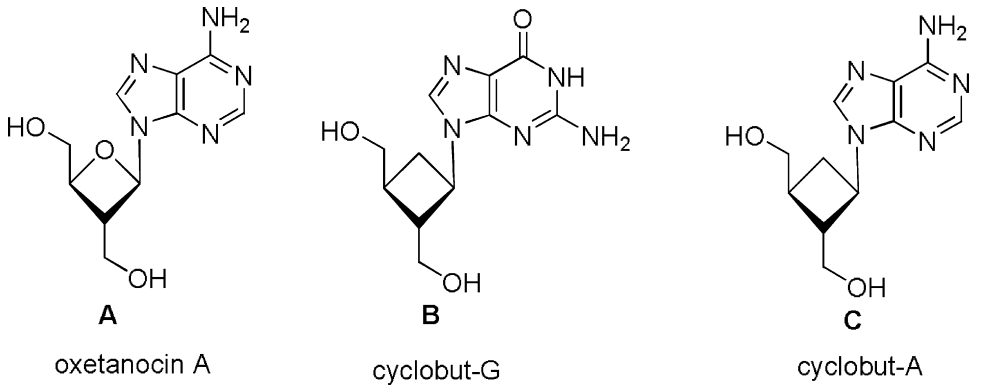
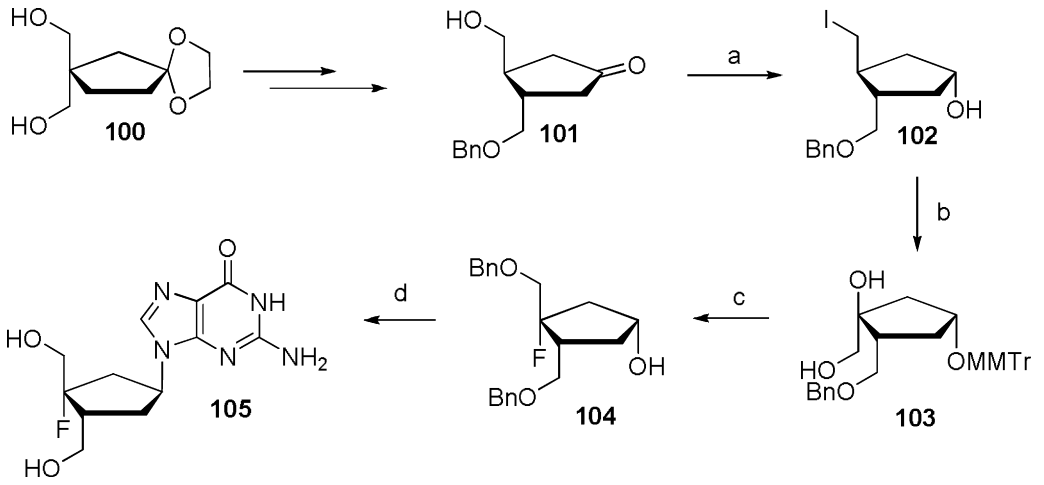
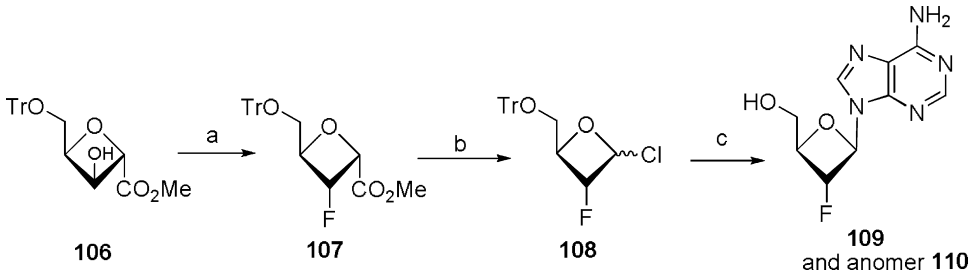


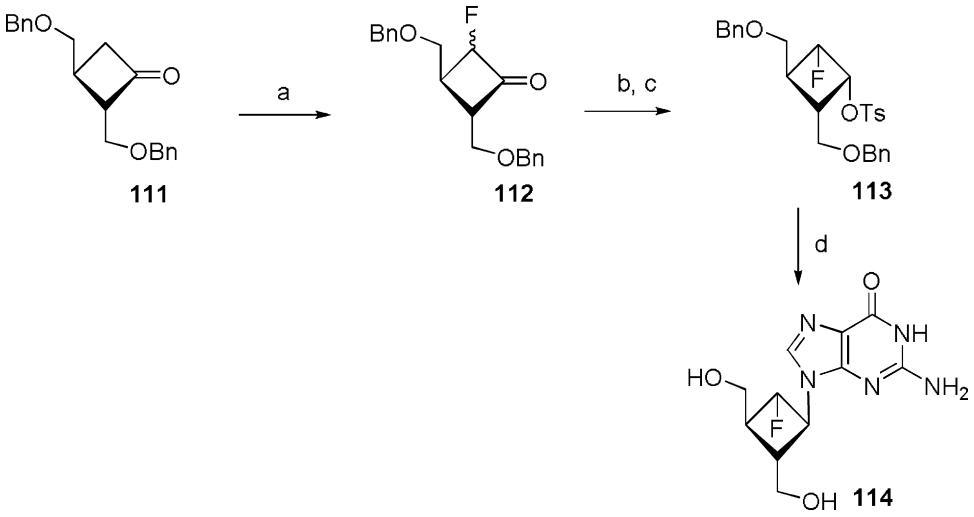
Fig. 4. Oxetanocin A and carbocyclic analogues.



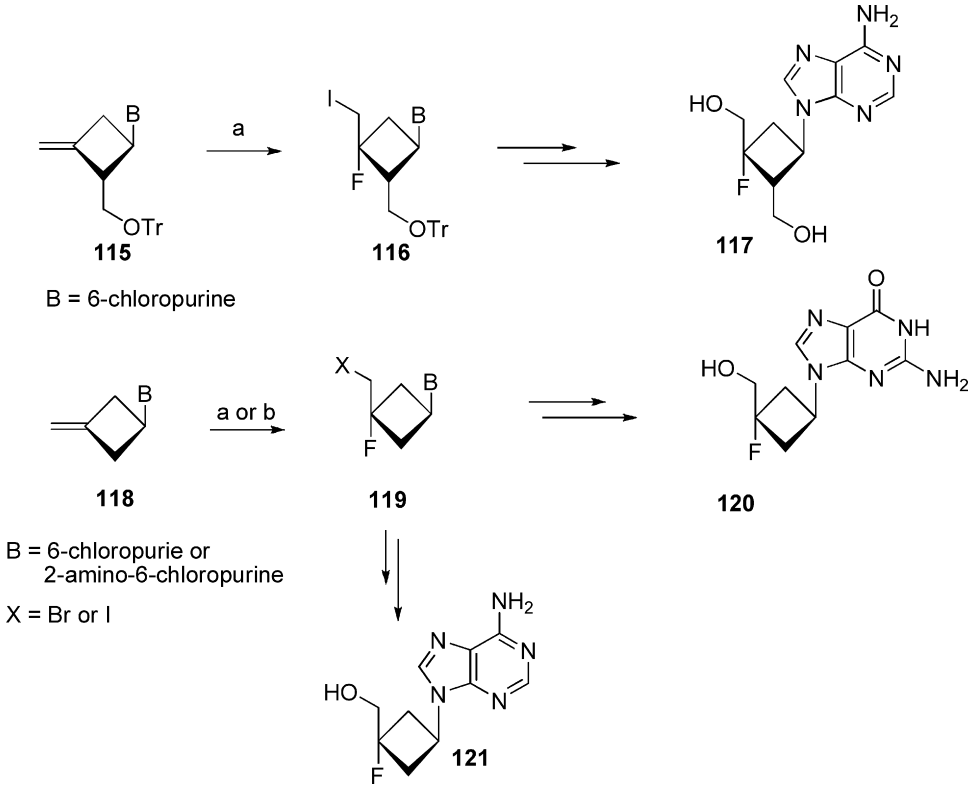
Scheme 20. Reagents: (a) i. $Me_4NBH(OAc)_3$, ii. ICH_2CH_2I, PPh_3, (b) i. DBU, toluene, ii. MMTrCl, DMAP, iii. K_2OsO_4, NMMO, (c) i. BnBr, NaH, ii. Deoxo-Fluor, pyridine, iii. *p*-TsOH, CH_2Cl_2 and (d) i. PPh_3, DIAD, 2-amino-6-chloropurine, ii. HCO_2H, NH_4OH, CH_3OH, iii. H_2, Pd black.



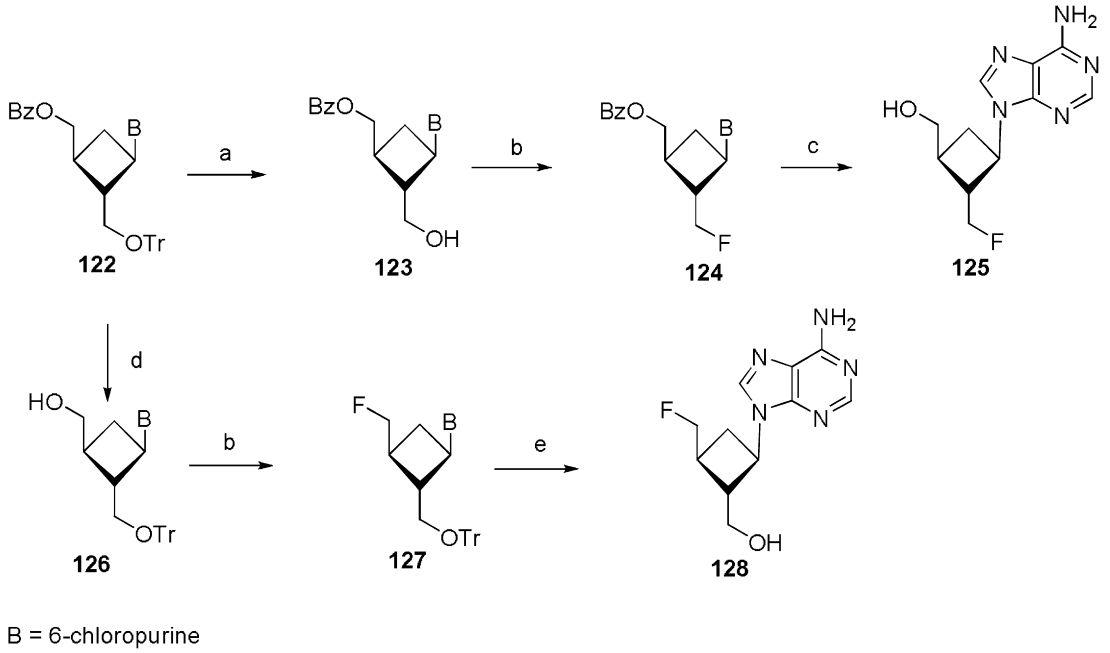
Scheme 21. Reagents and conditions: (a) DAST, (b) i. hydrolysis, ii. NCS, $Pb(OAc)_4$, AcOH, DMF and (c) i. adenine, ii. CF_3CO_2H, CH_3OH.



Scheme 22. Reagents: (a) LiTMP, $FClO_3$, (b) LS-selectride, (c) TsCl, pyridine and (d) i. 2-amino-6-phenylmethoxypurine, K_2CO_3, 18-Crown-6, ii. $Pd(OH)_2$, cyclohexane.



Scheme 23. Reagents: (a) I_2, AgF, THF and (b) i. NBS, KOH, AcOEt, H_2O, ii. DAST.

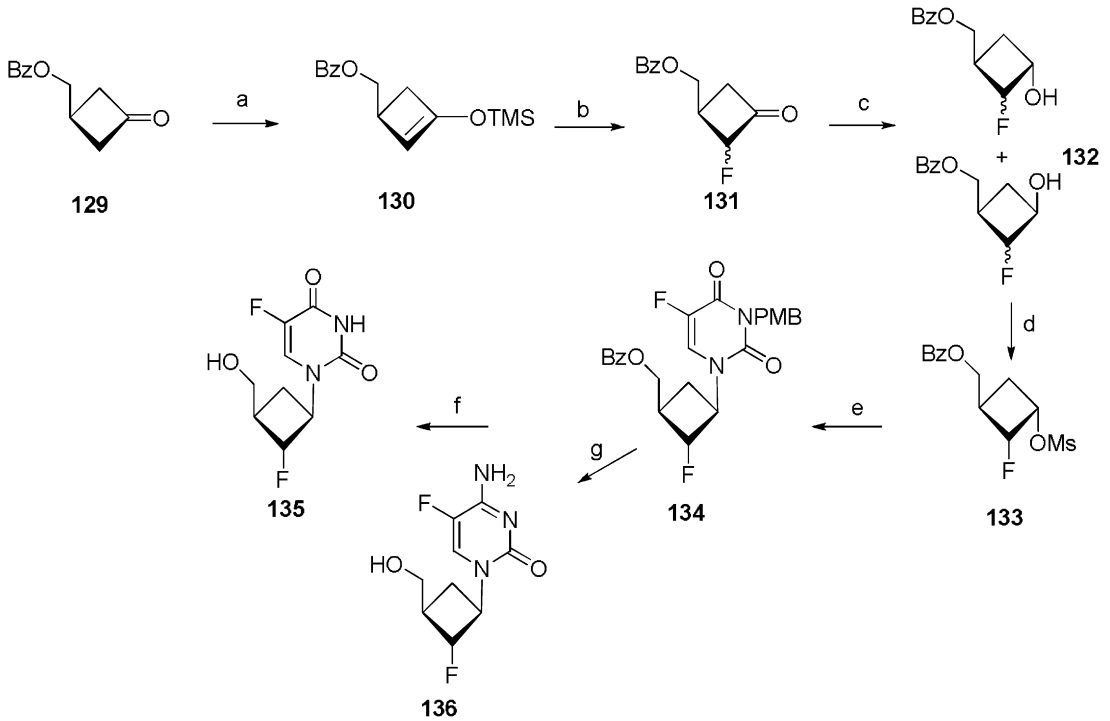


Scheme 24. Reagents: (a) CF_3CO_2H, (b) DAST, pyridine, (c) liq. NH_3, (d) 0.5 N NaOH, 1,4-dioxane and (e) i. liq. NH_3, ii. H^+.

to the carbonyl group of the intermediate **111** through treatment with LiTMP/$FClO_3$. After reduction of the resultant fluorinated ketone **112** and subsequent tosylation, the obtained compound **113** was subjected to nucleophilic substitution with 2-amino-6 phenylmethoxypurine and deprotection to afford cyclobutane nucleoside analogue **114** (Scheme 22) [43].

Legraverent and coworkers have accomplished the synthesis of the carbocyclic oxetanocin analogues **117**, **120** and **121** containing 3′-fluoro cyclobutyl moieties and different nucleobases. Compounds **116** and **119** were prepared from the olefinic precursors **115** and **118** either by the direct fluoro-iodination (AgF-I_2) or by DAST fluorination (Scheme 23) [44].

The C-2′ and C-3′ fluoromethyl analogues of adenosine, **125** and **128** were synthesized, starting from the intermediate compound **122**, which was converted into alcohols **123** and **126**, through treatment with NaOH and with 80% TFA, respectively (Scheme 24) [45]. DAST mediated fluorination of compounds **123** and **126** produced the fluorinated derivatives, **124** and **127**. The target nucleosides **125** and **128** were provided *via* ammonolysis of **124** and **127**.



Scheme 25. Reagents: (a) i. LDA, THF, ii. TMSCl, (b) Selectfluor, CH_3CN, (c) L-selectride, THF, (d) MsCl, pyridine, CH_2Cl_2, (e) K_2CO_3, 18-Crown-6, DMF, protected base, (f) $AlCl_3$, anisole and (g) i. 1-methylpyrrolidine, TMSCl, CH_3CN, ii. $(CF_3CO)_2O$, 4-nitrophenol, iii. NH_4OH, 1,4-dioxane.

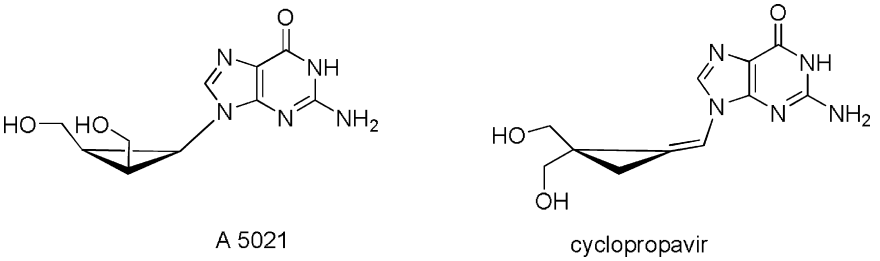


Fig. 5. Cyclopropanoid nucleosides A-5021 and cyclopropavir.

Recently, in 2007 Liotta and coworkers completed the synthesis of 2′-fluoro cyclobutyl nucleosides **135** and **136**, with fluorination of silyl enol ether **130** using Selectfluor (Scheme 25) [46]. After reduction of ketone **131**, the resultant major isomer **132** was mesylated to afford compound **133**. Coupling of mesylate **133** with protected 5-fluorouracil under basic conditions furnished nucleoside **134**, which was deprotected and subjected to base transformation to give the target fluorinated nucleosides **135** and **136**. The synthesized compounds were evaluated as anti-HIV agents.

2.3. Fluorinated cyclopropyl nucleosides

The cyclopropanoid nucleosides have not been of interest until compound A-5021 was discovered. 9-((1,2-Bis(hydroxymethyl)-cycloprop-1-yl)methyl)guanine (A-5021) was reported more active than acyclovir or penciclovir against HSV, HCMV and VZV (Fig. 5) [47].

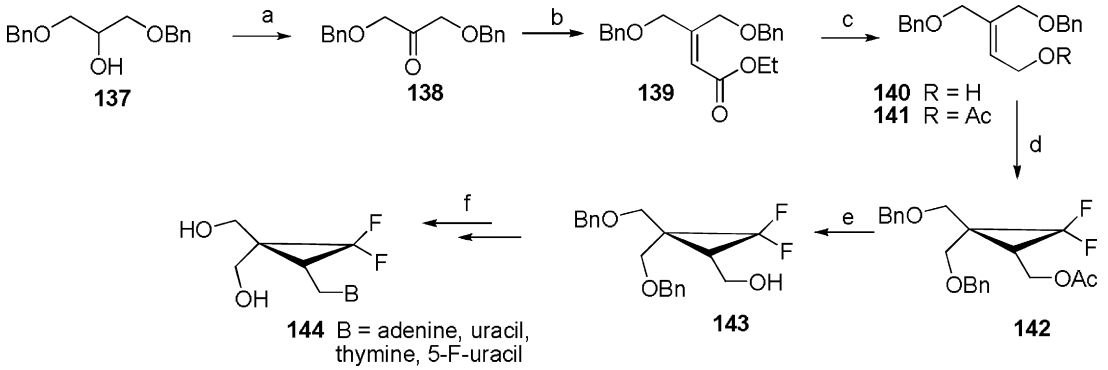
Csuk and Thiede have obtained novel difluorinated cyclopropane nucleoside analogues possessing both two vicinal hydroxymethyl groups and a methylene spacer between the nucleic acid base and the ring [48]. They started from alcohol **137** that was oxidized to the corresponding ketone **138**. Olefination of **138** furnished alkene **3** that upon treatment with diisobutylaluminium hydride resulted in the formation of alcohol **140** which was acetylated and the acetate **141** was subjected to a difluorocyclopropanation reaction to afford cyclopropane **142**. Treatment of **142** with catalytic amounts of sodium methoxide in methanol gave the key intermediate **143**. Reactions of **143** with triphenylphosphine, diethyl azodicarboxylate and protected nucleic acid base under Mitsunobu conditions afforded protected cyclopropane nucleoside analogues. The debenzoylationand and debenzylation processes afforded the analogues **144** (Scheme 26).

Kim and his group have designed and synthesized (*E*)-(1-fluoro-2-hydroxymethyl cyclopropylmethyl)purines and pyrimidines **150** [49]. An important step of their synthetic route was the introduction of fluorine and a double bond for the installation of the cyclopropyl group, achieved by the Horner–Wadsworth–Emmons reaction of aldehyde **145** with triethyl 2-fluoro-2-phosphonoacetate using *n*-BuLi. The allylic alcohol **146** was then subjected to ZnI_2-catalytic cyclopropanation to provide the cyclopropane derivative **147**. The subsequent N-alkylation of purine or pyrimidine bases with mesylate **148** or iodide **149** under basic condition was chosen as a convenient approach to the synthesis of the fluorocyclopropanoid nucleoside **150** (Scheme 27).

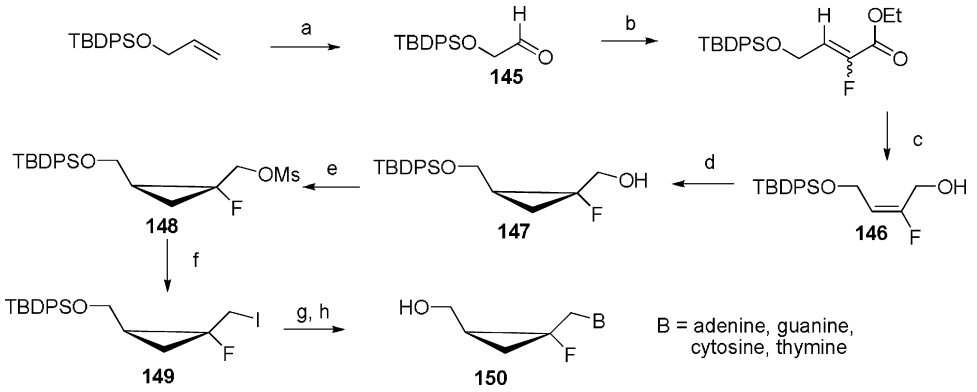
Later, Kim's group have accomplished the synthesis of [1′-fluoro-2′,2′-bis(hydroxymethyl)cyclopropylmethyl]purines **155 and 156** [50]. The introduction of a fluorine group was achieved by treating **151** with triethyl 2-fluoro-2-phosphonoacetate and *n*-BuLi using the Horner–Wadsworth–Emmons reaction. Cyclopropanation of the resultant allylic alcohol **152** was realized by a Lewis acid-catalyzed Furukawa modification of the Simmons–Smith reaction (Scheme 28). Mesylation of the fluorinated cyclopropyl alcohol **153** followed by iodination gave the precursor **154**. The coupling of iodide **154** with adenine or 2-amino-6-chloropurine in the presence of Cs_2CO_3 followed by removal of the protecting group afforded the target nucleoside **155**. The treatment of 2-amino-6-chloropurinyl derivative with 2-mercaptoethanol and sodium methoxide followed by hydrolysis with acetic acid gave nucleoside **156**. The synthesized nucleosides were evaluated for their antiviral activity against poliovirus, HSV-1, HSV-2, and HIV.

Hong's group also carried out the synthesis of C-fluoro branched cyclopropyl pyrimidine derivatives using similar procedures [51].

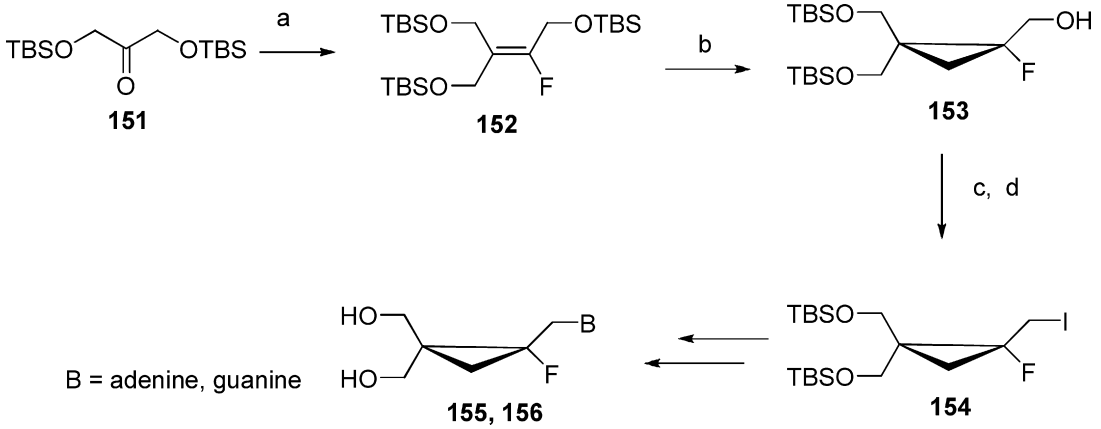
Haufe and coworkers synthesized a series of diastereopure monofluorinated cyclopropanoid nucleosides, **(Z)-165** and **(E)-164**, using another synthetic route (Scheme 29) [52]. They started from fluorostyrene **157**, which was converted into the racemic separable esters **(E)-159** and **(Z)-158** by reaction with diazoacetate. After reduction with $LiAlH_4$ and acetylation, the resultant acetates **(E)-161** and **(Z)-160** served as precursors for the cyclopropanoid nucleosides. They were subjected to oxidation with catalytic amount of $RuCl_3$ in combination with $NaIO_4$ and subsequent reduction with $BH_3{\cdot}SMe_2$ to afford alcohols **(E)-163** and **(Z)-162**. Direct coupling with the nucleobases under



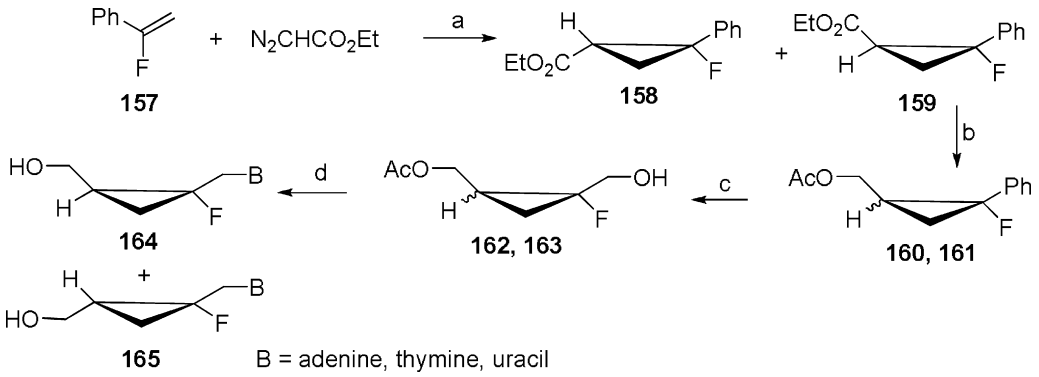
Scheme 26. Reagents and conditions: (a) TEMPO, (b) olefination, (c) DIBAH, (d) $ClCF_2CO_2Na$, diglyme, (e) CH_3ONa, CH_3OH and (f) base installation and deprotection.



Scheme 27. Reagents: (a) i. O_3, CH_2Cl_2–CH_3OH, ii. $(CH_3)_2S$, (b) $(C_2H_5O)_2(O)PCHFCO_2C_2H_5$, *n*-BuLi, THF, (c) DIBAL-H, CH_2Cl_2, (d) $Zn(C_2H_5)_2$, CH_2I_2, *in situ* ZnI_2, CH_2Cl_2, (e) MsCl, pyridine, (f) NaI, (g) NaH, base, DMF and (h) $BuNF_4$, THF.



Scheme 28. Reagents: (a) i. $(C_2H_5O)_2(O)PCHFCO_2C_2H_5$, *n*-BuLi, THF, ii. DIBAL-H, CH_2Cl_2, (b) $Zn(C_2H_5)_2$, $Zn(CH_2I)_2$, *in situ* ZnI_2, CH_2Cl_2, (c) MsCl, TEA and (d) NaI, acetone.

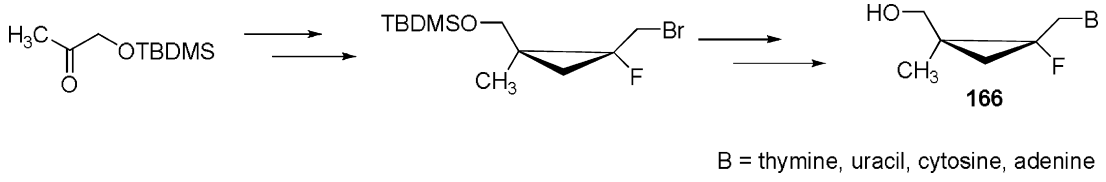


Scheme 29. Reagents: (a) $Cu(acac)_2$, (b) i. $LiAlH_4$, AcCl, TEA, (c) i. $RuCl_3{\cdot}H_2O$, $NaIO_4$, ii. $BH_3{\cdot}S(CH_3)_2$, Et_2O and (d) i. PPh_3, DEAD, protected bases, ii. NH_3, CH_3OH.

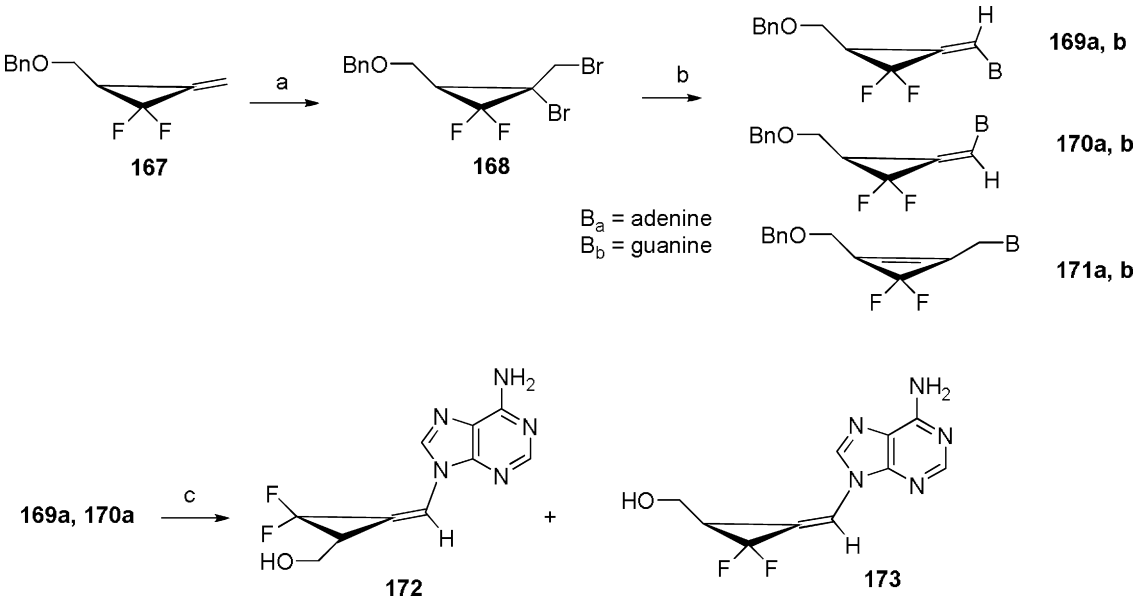
Mitsunobu conditions and subsequent deprotection with NH_3/MeOH provided the desired monofluorinated cyclopropanoid nucleosides **(Z)-165** and **(E)-164**.

Moreover, Hong synthesized and tested against several viruses such as the HIV, HSV-1, HSV-2 and HCMV some C-fluoro branched cyclopropyl nucleosides **166**. This classes of nucleosides were designed and synthesized to evaluate them against various viruses (Scheme 30) [53]. Their synthetic procedures were similar to those described before [50].

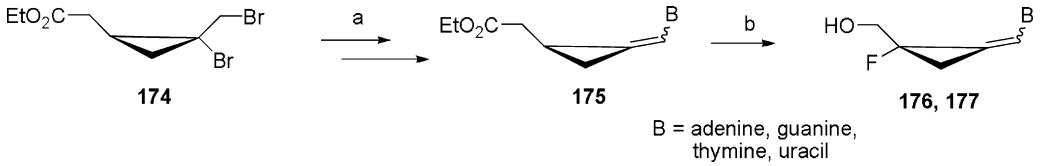
The (*Z*)-methylenecyclopropane analogues of purine nucleosides are effective antiviral agents. Especially, the guanine analogue, cyclopropavir (Fig. 5), is treated as a possible drug



Scheme 30. Monofluorinated cyclopropyl nucleosides.



Scheme 31. Reagents: (a) HBr_3·pyridine, CH_2Cl_2, (b) purines, NaH, DMF and (c) BCl_3, CH_2Cl_2.



Scheme 32. Reagents: (a) nucleobases or their precursors, K_2CO_3 and (b) i. LiCl, LDA, ii. NFSI, THF, iii. KI, TMSCl or reduction.

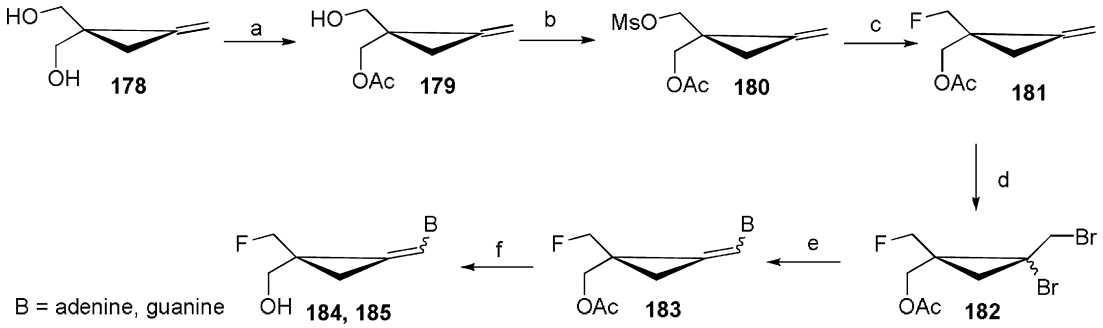
against infections caused by human cytomegalovirus (HCMV) [54].

In 2001 Zemlicka and coworkers first reported the synthesis and antiviral activity of methylenedifluorocyclopropane analogues of nucleosides [55]. The key reagent **168** for alkylation-elimination procedure with nucleic acid bases was obtained by addition of bromine (using pyridinium hydrobromide perbromide) to the known methylenedifluorocyclopropane **167**. Reaction of **168** with sodium salt of adenine in DMF afforded a mixture of products **169a**–**171a** which were separated by column chromatography. Deprotection of **170a** and **169a** using BCl_3 afforded the target analogues **172** and **173** (Scheme 31).

In the synthesis of *Z* and *E* isomers of fluoromethylenecyclopropane nucleoside analogues **176** and **177** Zemlicka and coworkers used the methylenecyclopropane ester **175** obtained in alkylation-elimination reactions between dibromide **174** and the corresponding nucleic bases or precursors (Scheme 32) [56]. Selective monofluorination of compounds **175** using N-fluorobenzenesulphonimide followed by reduction of the ester moiety gave the target nucleosides, **(Z)-176** and **(E)-177**.

The *geminal* difluoro analogues, except adenine derivative, do not show antiviral activity. By contrast, monofluoro derivatives **176**, **177** exhibited varying degree of antiviral effects particularly against HCMV, VZV and HIV-1.

In 2008, purine fluoromethylenecyclopropane analogues **184a**, **184b**, **185a**, and **185b** were synthesized by Zemlicka and his group as potential antiviral agents (Scheme 33) [57]. Methylenecyclopropane diol **178** was chosen as a convenient starting material for the synthesis of analogues **184** and **185**. Acetylation of **178** gave monoacetate **179**. Compound **179** was converted to methylsulphonate **180** using methylsulphonyl chloride which was smoothly transformed to fluorocyclopropane **181** using TBAF. Addition of bromine *via* pyridinium tribromide gave dibromo derivative **182** which was used in the reaction with nucleobases. The reaction of **182** with adenine gave a mixture of *Z*- and (*E*)-isomers of methylenecyclopropanes **183**. Deacetylation of **183** using K_2CO_3



Scheme 33. Reagents: (a) i. $CH_3(OCH_3)_3$, TsOH, CH_2Cl_2, ii. Et_3N, iii. AcOH, (b) MsCl, Et_3N, CH_2Cl_2, (c) Bu_4NF, THF, (d) HBr_3·pyridine, CH_2Cl_2, (e) purines, K_2CO_3, DMF and (f) K_2CO_3, CH_3OH–H_2O.

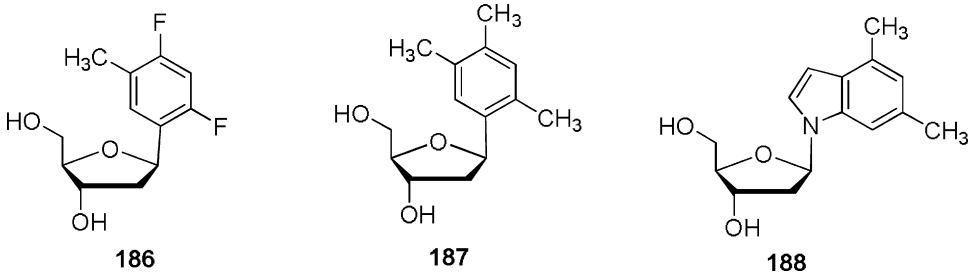


Fig. 6. Isosteres of thymidine and 2-aminodeoxyadenosine.

furnished after chromatographic separation the target analogues **184** and **185**.

The obtained compounds were tested against HCMV, VZV, HIV-1, HBV and HCV viruses and the adenine analogue **184a** was the most potent and least cytotoxic.

3. Fluorinated analogues of nucleosides with modified base

Nucleic acids show a great variety of secondary structures. All these structures are stabilized mainly by interactions of purine and pyrimidine bases with their neighbours. The interaction most important for the stability of nucleic acids is hydrogen bonding. Also stacking of the bases plays a significant role in the stability of the duplex RNA and DNA double helix. Because nucleic acid bases are limited to four predominant structures and a few closely related analogues, there is a limited number of available probes which can be used to investigate the parameters which contribute to base pairing. Chemically modified bases are frequently used to stabilize nucleic acids, to study the driving forces for nucleic acid structure formation. Non-natural analogues of nucleosides have been widely useful in probing important noncovalent interactions with other molecules, including metals, small organic compounds, proteins and other nucleic acids.

3.1. Fluorinated aromatic analogues of nucleosides

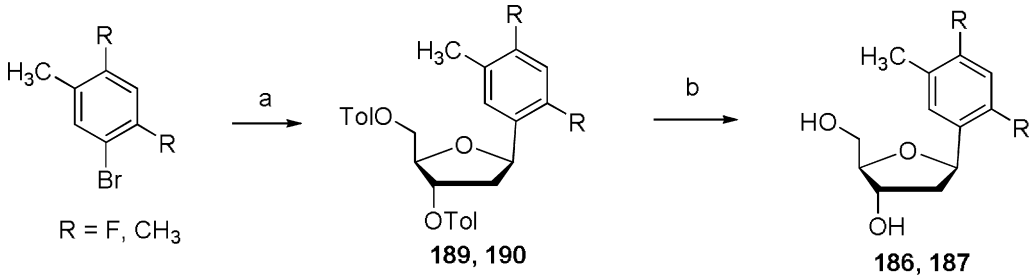
A series of aromatic apolar nucleoside analogues as isosteres of natural nucleosides have been proposed, in which the steric shape was conserved as closely as possible, but the polar functionality was removed. The best isosteric replacement of C=O functionality is the C–F group because of nearly identical bond lengths [58], C–H groups replace N–H groups and CH_3 replaces NH_2. These replacements were intended to abolish or greatly limit the ability of these compounds to undergo hydrogen bonding that occurs naturally in nucleic acids. Several authors studying modified DNAs have established that it is possible to design nonpolar nucleobase analogues that exhibit selective and stable pairing in the absence of hydrogen bonding.

Kool was the first to observe that H-bonds are not absolutely necessary for efficient base-pairing and introduced a new concept of hydrophobic interactions. In 1994 he described the synthesis and structures of aromatic nucleoside isosteres which may be used as probes of noncovalent bonding in DNA and as replacements for the natural nucleosides in designed nucleic acid structures [59]. They designed analogues **186** and **187** as isosteres of thymidine, and nucleoside **188** is an isostere of 2-aminodeoxyadenosine, the triply-bonded Watson-Crick partner of thymidine (Fig. 6).

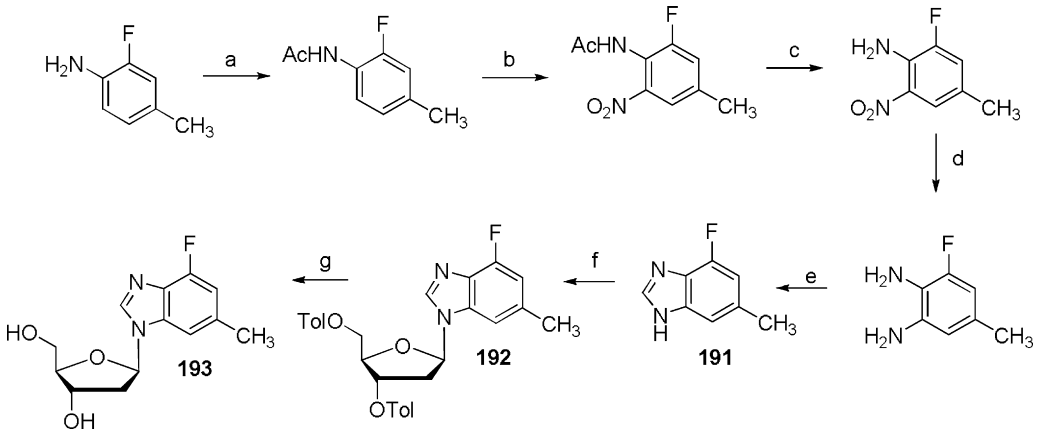
The strategy for formation of the glycosidic bonds for the C-nucleoside analogues relied on coupling of aryl Grignards with an α-chloro-substituted deoxyribose derivative. The subsequent deprotection of **189** and **190** with sodium methoxide in methanol gave nucleoside isostere **186** and **187** (Scheme 34).

Difluorotoluene nucleoside **186** as a nonpolar mimic for natural thymidine cannot measurably form paired complexes with adenine derivatives and should not serve as a template for replication. However Kool and coworkers have shown, that a DNA polymerase can exert high fidelity even when a base pair completely lacks conventional hydrogen bonds and that nucleoside **186** serves as a very good template for DNA synthesis. The nonpolar aromatic analogue behaved similarly to thymidine despite its poor hydrogen bonding ability [60]. They hypothesized that the reason why analogue **186** is so successful in DNA replication is that it retains the steric shape and conformation of the natural nucleoside.

Kool has further continued the systematic research on fluorinated aromatic nucleosides. The preparation and structure of deoxyribonucleoside of 4-fluoro-6-methylbenzimidazole, abbreviated dH (**193**), which acts as a close shape mimic of nucleoside deoxyguanosine was reported in 2002 [61]. They find that it stacks surprisingly strongly in DNA, and it selectively pairs with previously described analogue **186** (dF), resulting in a fully hydrophobic, non-H-bonded pair (H–F) that mimics the natural G–T mismatch quite closely. Starting with commercial 2-fluoro-4-methylaniline, the nucleobase mimic 4-fluoro-6-methyl-1*H*benzimidazole **191** was synthesized in five steps. Benzimidazole **191** was then coupled with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-R-D-*erythro*-pentafuranose in the presence of sodium hydride. The two resulting isomers **192** were then deprotected with sodium methoxide and separated by column chromatography to yield 5-(4-fluoro-6-methylbenzimidazol-1-yl)-β-D deoxyriboside **193** (Scheme 35).



Scheme 34. Reagents: (a) i. Mg, THF, ii. α-chloro substituted deoxyribose derivative and (b) CH_3ONa, CH_3OH.



Scheme 35. Reagents: (a) Ac_2O, $CHCl_3$, (b) HNO_3, (c) KOH, CH_3OH, (d) H_2, Pd/C, (e) HCO_2H, (f) NaH, CH_3CN, α-chloro substituted deoxyribose derivative and (g) CH_3ONa, CH_3OH.

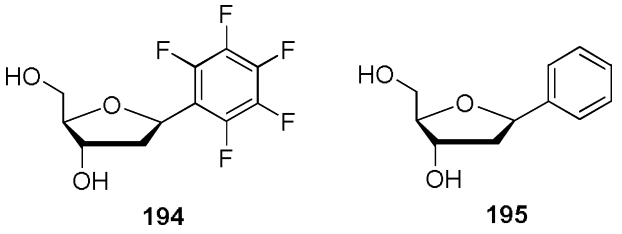


Fig. 7. Pairs of pentafluorophenyl-β-D-deoxyriboside and phenyl-β-D-deoxyriboside as aromatic nucleoside analogues.

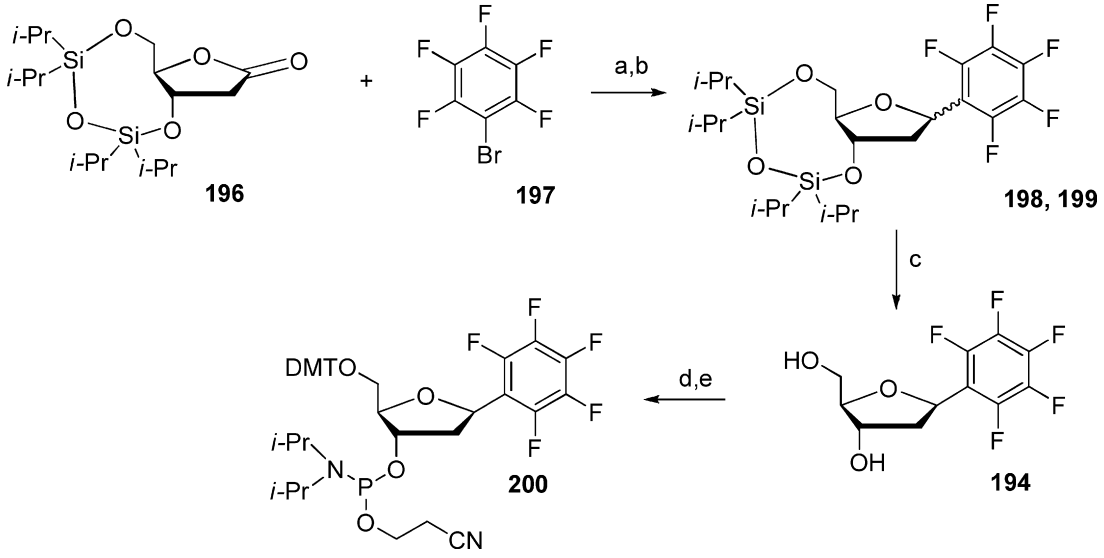
Nucleoside **193** was converted to the standard 5′-*O*-dimethoxytrityl-3′-*O*-cyanoethylphosphoramidite derivative in preparation for automated DNA synthesis. Incorporation into oligodeoxynucleotides was carried out with standard coupling cycles.

Matiz and Hunziker described pentafluorobenzene as a nucleobase analogue [62]. This was initially conceived as a useful perfluorinated derivative for studying hydrophobic and stacking effects in nucleic acids. Pairs of pentafluorophenyl-β-D-deoxyriboside (F^5, **194**) and phenyl-β-D-deoxyriboside (P, **195**) were used to investigate the stability of F^5-P base pairs in oligonucleotide duplexes (Fig. 7).

The synthesis of pentafluorophenyl congener **194** was shown in Scheme 36. Bromopentafluorobenzene **197** was lithiated and then the silyl-protected 2-deoxyribonolactone **196** was added. The resulting hemiacetal was reduced to give a mixture of the two anomers **198** and **199**. These compounds could be separated by chromatography after deprotection of the deoxyribose moiety and reprotection as 5′-dimethoxytrityl ethers. The pentafluorophenyl-β-D-riboside phosphoramidite **200** was then obtained by standard phosphitylation. Oligonucleotides containing **194** and **195** were prepared using a regular solid-phase DNA synthesis protocol.

However, perfluorinated derivative as an analogue of nucleic acids base causes some destabilization and a tetrafluorbenzene variant was shown to have more favourable properties. More recent studies described selective "fluorous" effects at the active site of a DNA polymerase, by using analogues 2,3,4,5-tetrafluorobenzene and 4,5,6,7-tetrafluoroindole [63]. The 5′-triphosphate deoxynucleotide derivatives of DNA base analogues 2,3,4,5-tetrafluorobenzene (^{F}**B 203**) and 4,5,6,7-tetrafluoroindole (^{F}**I 201**), as well as hydrocarbon controls benzene (**B 204**) and indole (**I 202**), were synthesized and studied as substrates for the DNA Polymerase I Klenow fragment (KF exo-) (Fig. 8).

The purine like fluorinated indole nucleotide ^{F}**I 201** was the most efficiently inserted of the four hydrophobic analogues, with the most effective incorporation occurring opposite the pyrimidine-like tetrafluorobenzene ^{F}**B 203**. In all cases, the polyfluorinated base pairs were more efficiently processed than the



Scheme 36. Reagents: (a) BuLi, Et_2O, (b) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, (c) Bu_4NF, THF, (d) DMT-Cl, DMAP, pyridine and (e) [(*i*Pr_2N)(NCCH_2CH_2O)P]Cl, *i*Pr_2NEt, THF, DMT.

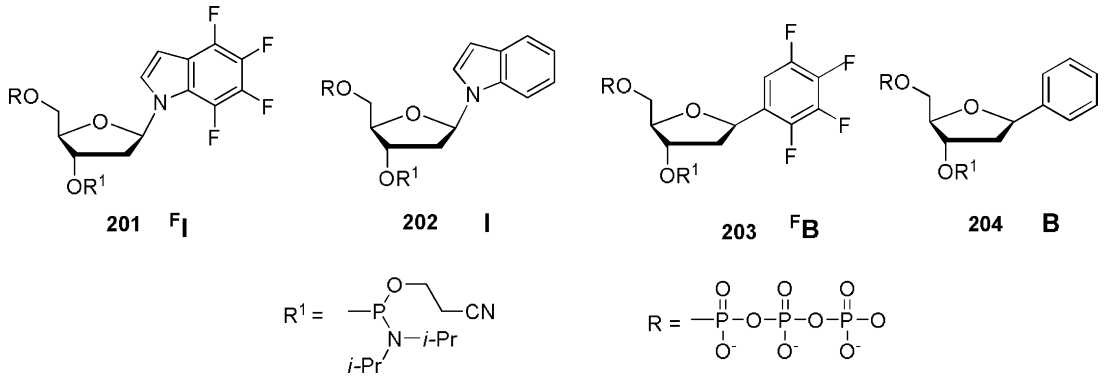
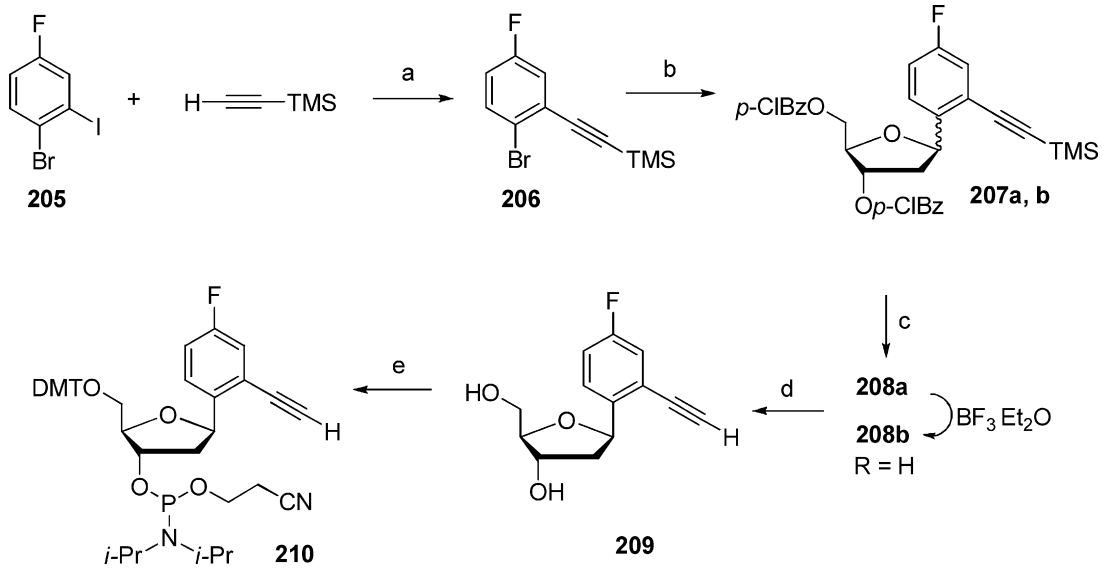


Fig. 8. The 5′-triphosphate deoxynucleotide analogues.



Scheme 37. Reagents: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, (b) i. Mg, THF, ii. $CdCl_2$, iii. α-chloro substituted deoxyribose derivative, (c) TBAF, (d) CH_3ONa, CH_3OH and (e) i. DMT-Cl, ii. $NCC_2H_4OP(N\text{-}iPr_2)_2$, DIPAT.

analogous hydrocarbon pairs. Their results strongly suggested that polyfluorination can generally increase polymerase activity of nonpolar nucleotide derivatives by the increased hydrophobicity.

Griesang and Richert synthesized oligonucleotides containing a nucleotide analogue with an ethynyl fluorobenzene as a nucleobase surrogate [64]. Modified analogues of nucleobases may engage in duplex stabilizing interactions by forming additional hydrogen bonds, by binding *via* the major or the minor groove, or by offering additional surface sites for stacking. The protected 3′-phosphoramidite **210** was prepared and employed in the synthesis of oligonucleotides. The DNA duplex with ethynylfluorobenzene-containing nucleotide showed UV-melting point higher than the duplex containing a difluorotoluene moiety. Synthesis of phosphoramidite **210** (Scheme 37) started from **205** by Sonogashira coupling with trimethylsilylacetylene giving bromide **206**. The bromide was converted to its Grignard derivative and reacted with chloroglycosyl sugar to yield a mixture of **207a** and **207b**. The desilylation to **208a** and **208b** allowed chromatographic separation, followed by epimerization of **208a**. Desired β-epimer **208b** was deprotected to **209**, protected with a dimethoxytrityl group and phosphitylated to obtain **210**.

The ribonucleosides with 2,4-difluorobenzene and 4,6-difluorobenzimidazole as fluoro modified universal nucleobases were also synthesized and investigated in RNA duplexes and compared to the oligoribonucleotides carrying benzene or benzimidazole modification, respectively [65–67]. CD and UV spectra show that the incorporation of modified nucleosides does not lead to changes in the structure of RNA. The substitution of the natural nucleosides

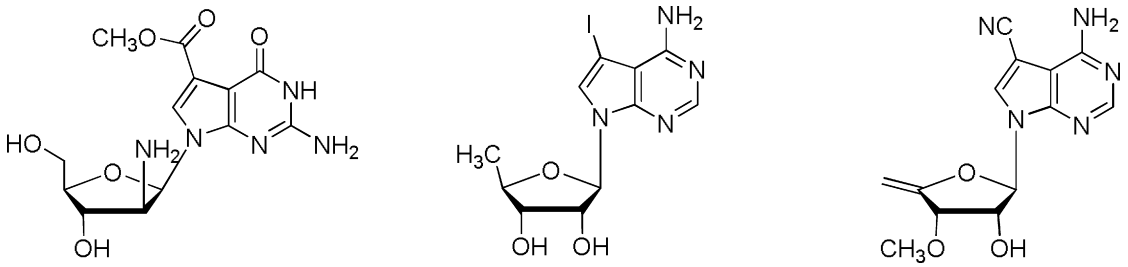


Fig. 9. Structures of naturally occurring 7-deazapurine deoxyribonucleosides.

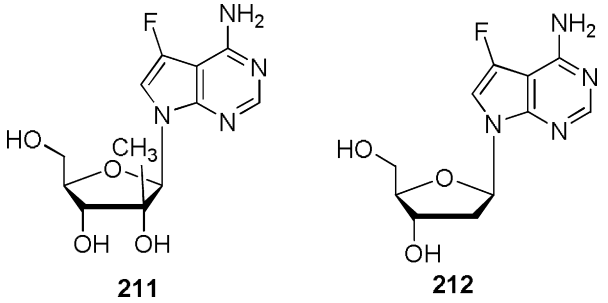


Fig. 10. Fluorinated derivatives of tubercidin.

with aromatic fluorinated analogues results in a better catalytic activity or at last only small reduction of the catalytic efficiency of the ribozyme compared to the unmodified one.

3.2. Fluorinated deazapurine nucleosides

7-Deazapurine (pyrrolo[2,3-*d*]pyrimidine) ribonucleosides have found widespread applications in chemistry, physics, and biology. In contrast to the naturally occurring 7-deazapurine ribonucleosides, the corresponding 2′-deoxyribonucleosides are not found in nature, except a few deoxynucleosides with very particular sugar structure (Fig. 9).

It had been recognized that the shape of 7-deazapurine 2′-deoxyribonucleosides resembles closely that of purine nucleosides found in duplex DNA. Stable Watson–Crick base pairs are formed between 7-deazapurines and complementary pyrimidines within oligonucleotide duplexes showing similar base stacking as those of canonical DNA bases. The strongly stabilizing effect on DNA makes 7-deazapurines good candidates for primers or probes used in DNA diagnostics, sequencing and also very useful for antisense technology. They are substrates or inhibitors of various enzymes acting on the nucleoside level, on 2′-deoxyribonucleoside triphosphates or on nucleic acids. 7-Substituted purines are positively charged, while 7-substituted 7-deazapurines are neutral being well accepted by DNA polymerases. Moreover, the C-7 position of 7-deazapurine nucleosides is an ideal place to introduce functionalities, as this site lies in the major groove of DNA [68]. The halogen substituents introduced at position C-7 greatly increase the duplex stability.

The C-2′ methyl derivative **211** of 7-fluorotubercidin is one of the most potent and selective inhibitors of HCV polymerase [69]. 7-Fluorinated 2′-deoxytubercidin **212** was synthesized [70], and X-ray analyses were performed showing the influence of the fluoro substituent on the nucleoside conformation [71] (Fig. 10).

Seela and coworkers obtained a series of 7-deaza-7-fluoropurine-2′-deoxynucleosides as well as 2′-deoxy-2′-fluoroarabinofuranosyl nucleosides [70,72]. The fluorine atom was introduced on the base level with Selectfluor. The nucleobase-anion glycosylation afforded the 7-fluorinated-7-deaza-inosine derivatives **213**, and the 7-deaza-7-fluoro-2′-deoxyguanosine **214**. 7-Deazapurine 2′-deoxyribonucleosides **213a** and **214** were converted into the corresponding phosphoramidites **215** and **216** by standard procedures (Fig. 11).

The synthesis of 7-deaza-2′-deoxy-7-fluoroguanosine **214** is shown in Scheme 38. It started from the 7-fluorinated 7-deazapurine base **218**. The latter was obtained from the 2-pivaloyl derivative **217** which was fluorinated regioselectively at position C-7 using Selectfluor in the presence of acetic acid. The glycosylation of **218** with sugar halide furnished the protected nucleoside **219**. Deprotection and displacement of the 6-chloro group yielded 6-methoxy compound **220**, which was transformed afterwards with 2 N NaOH to 2′-deoxyguanosine analogue **214**.

Later Seela synthesized a series of 7-fluorinated 7-deazapurine 2′-deoxyribonucleosides related to deoxyxanthosine, and 2′-deoxyisoguanosine [73]. The C-7 fluoro substituent was introduced in 2,6-dichloro-7-deaza-9H-purine **221** with Selectfluor. Apart from 2,6-dichloro-7-fluoro-7-deaza-9H-purine **222**, 7-chloro compound **223** was formed as by-product and the mixture was used for further glycosylation to **224**.

The 7-fluoro- and the 7-chloro-7-deaza-2′-deoxyxanthosine **226** was obtained from the corresponding methoxy compound **225** (Scheme 39). The 2′-deoxyisoguanosine derivative **228** was prepared from 2-chloro-7-fluoro-7-deaza-2′-deoxyadenosine **227** *via* a photochemically induced nucleophilic displacement reaction (Scheme 40).

The solid-liquid nucleobase anion glycosylation was applied in the synthesis of 7-deaza-2′-deoxy-2-fluoroadenosine **232** (Scheme

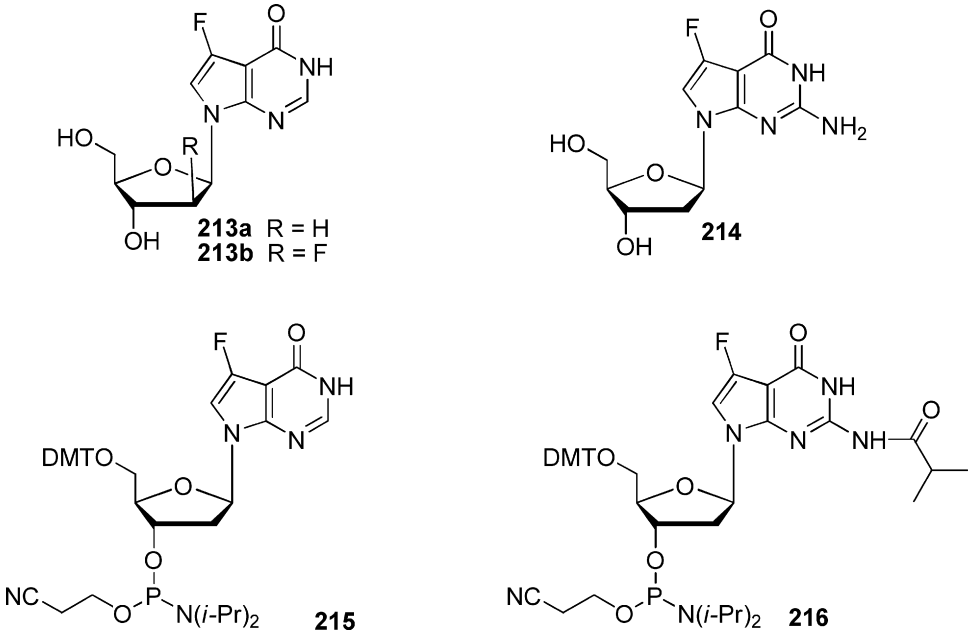
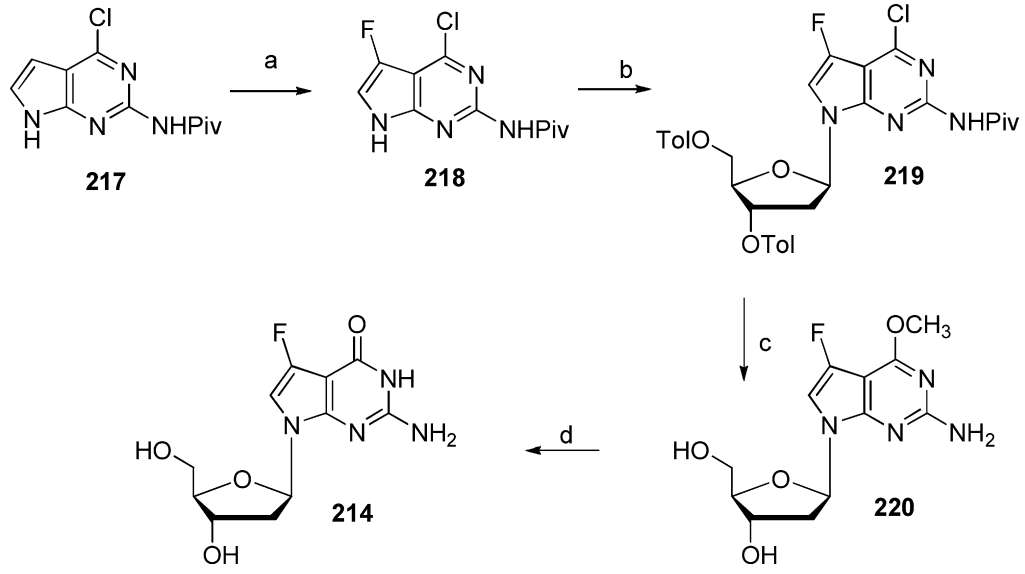
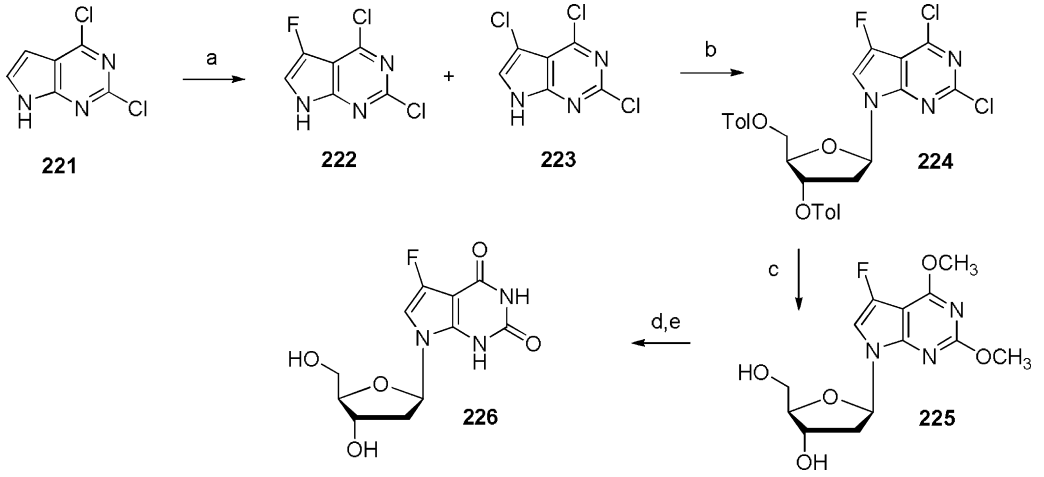


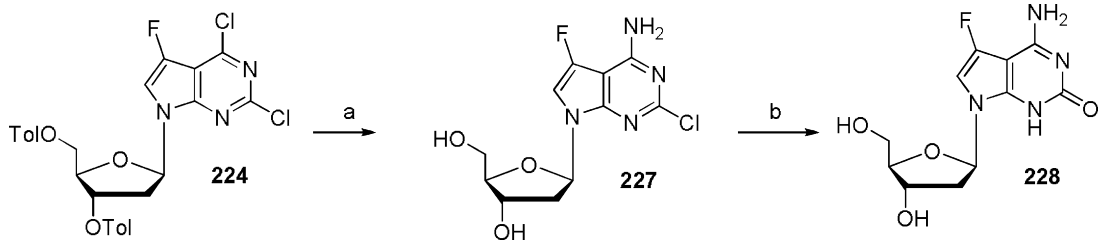
Fig. 11. 7-Fluorinated-7-deaza inosine and deoxyguanosine derivatives and their corresponding phosphoramidites.



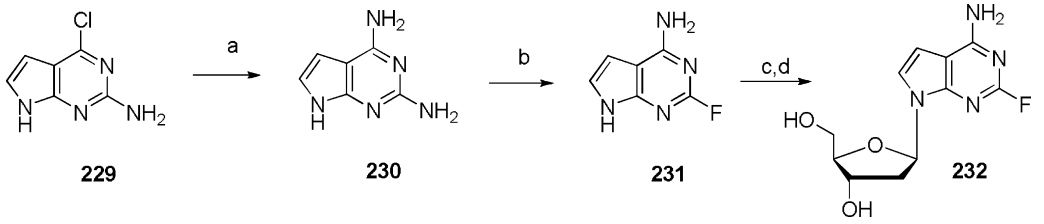
Scheme 38. Reagents: (a) Selectfluor, CH_3CN, AcOH, (b) α-chloro-sugar, CH_3CN, KOH, TDA-1, (c) CH_3ONa, CH_3OH and (d) 2 N NaOH.



Scheme 39. Reagents: (a) Selectfluor, CH_3CN, AcOH, (b) KOH, TDA-1, CH_3CN, (c) 0.5 M CH_3ONa, CH_3OH, (d) 2 N NaOH and (e) TMSCl, NaI, CH_3CN.



Scheme 40. Reagents: (a) NH_3, CH_3OH and (b) 0.1% NH_3/H_2O, $h\nu$.



Scheme 41. Reagents: (a) aq. NH_3, dioxane, (b) HF, pyridine, t-$BuNO_2$, (c) TDA-1, KOH, CH_3CN and (d) NH_3, CH_3OH.

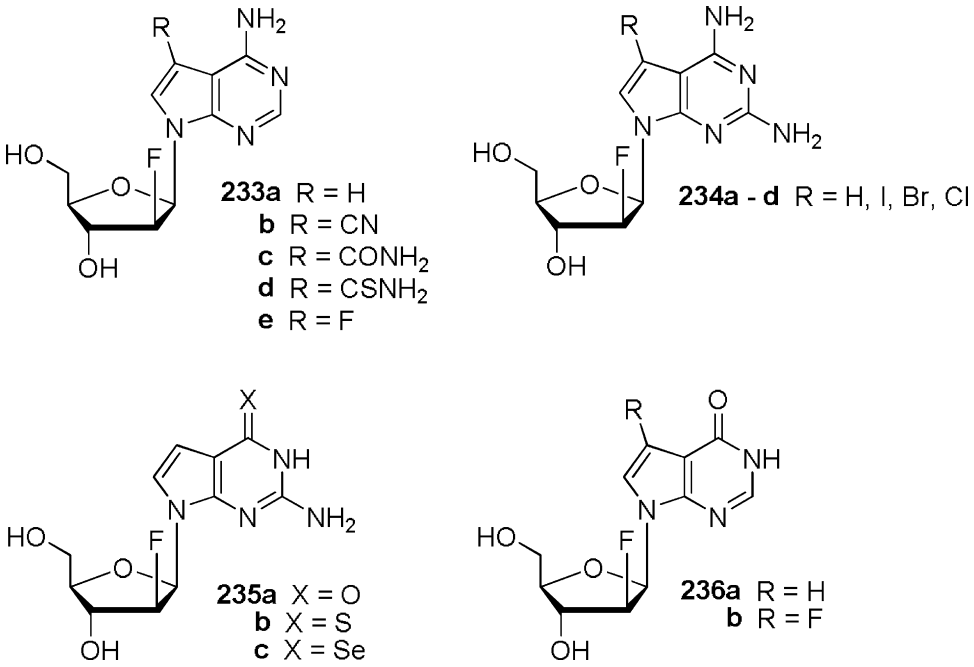


Fig. 12. Selected 7-deazapurine fluoroarabinonucleosides.

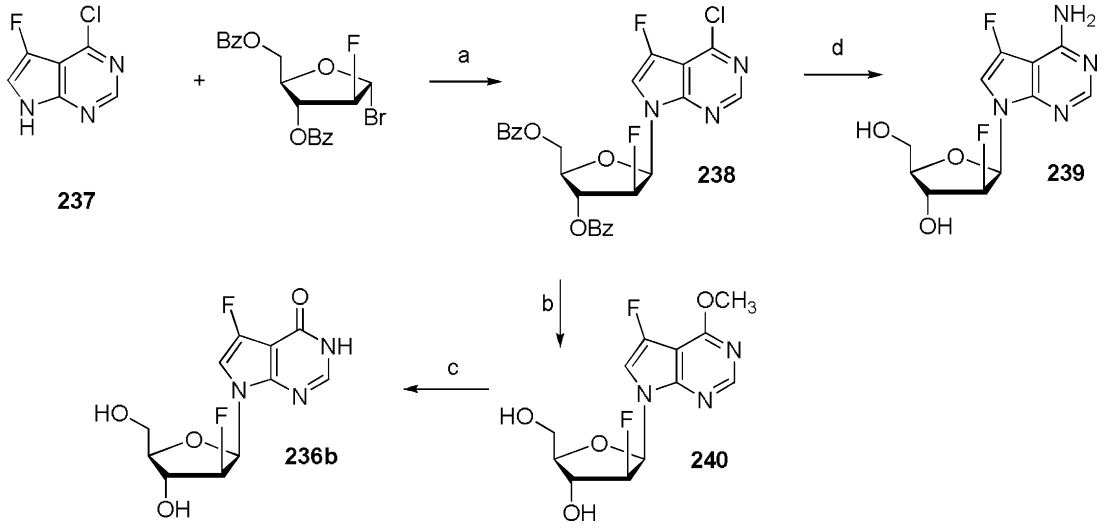
41) [74]. Therefore, the corresponding nucleobase **230**, obtained from 2-amino-6-chloro-7-deazapurine **229**, was used. The diazotization/fluorination reaction was performed in HF/pyridine by dropwise addition of *t*-$BuNO_2$ resulting in the 2-fluoro derivative **231**. Glycosylation of **231** afforded the toluoyl-protected β-D-nucleoside which was deprotected in methanolic ammonia to give 7-deaza-2′-deoxy-2-fluoroadenosine **232**.

It has been shown that the sugar modification of nucleosides by a fluorine atom can enhance biological activity as well as the stability of glycosyl bond. Fluorinated 7-deazapurine nucleosides, such as 2′-deoxy-2′-fluoroarabinosangivamycin **233c** and 2-amino-2′-deoxy-2′-fluoroarabinotubercidin **234a**, can act as antiviral agents [75,76]. Selected 7-deazapurine fluoroarabinonucleosides **233**–**236** are shown in Fig. 12. These nucleosides were synthesized by a convergent route using the nucleobase anion glycosylation. This reaction utilized a 7-deazapurine base which was glycosylated with 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide [77].

A reaction sequence is outlined in Scheme 42. The solid-liquid glycosylation of 6-chloro-7-deaza-7-fluoropurine **237** with the sugar (TDA-1/KOH/MeCN) resulted in the formation of α-D-nucleoside **238**. The latter was deprotected in ammonia with the concomitant displacement of C-6 chloro substituent by an amino group affording the fluorinated tubercidin derivative **239**. Compound **238** was also transformed to 6-methoxy compound **240** and demethylated with 2 N NaOH to gave the inosine analogue **236b** [70].

Very recently, in 2011, Chang and coworkers synthesized and tested for anti-HIV-1 activity 4-subsituted-7-(2′-deoxy-2′-fluoro-4′-azido-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine analogues. Initial biological studies indicated that among these ribonucleoside analogues, 4-amino-5-fluoro-7-(2′-deoxy-2′-fluoro-4′-azido-β-D-ribofuranosyl)pyrrolo [2,3-d]pyrimidine **241** (Fig. 13), showed moderate activity and no significant cytotoxicity [78].

Also Hocek and his group have synthesized a series of novel 7-deazapurine ribonucleosides bearing an alkyl, aryl, or hetaryl



Scheme 42. Reagents: (a) TDA-1, KOH, CH_3CN, (b) CH_3ONa, CH_3OH, (c) 2 N NaOH and (d) aq. NH_3.

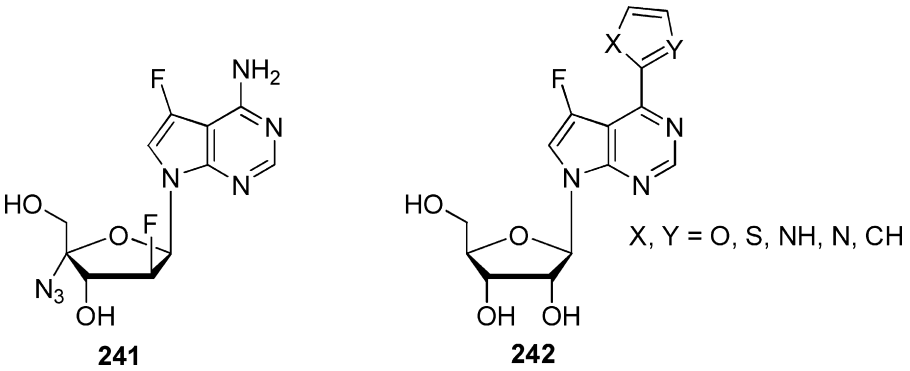
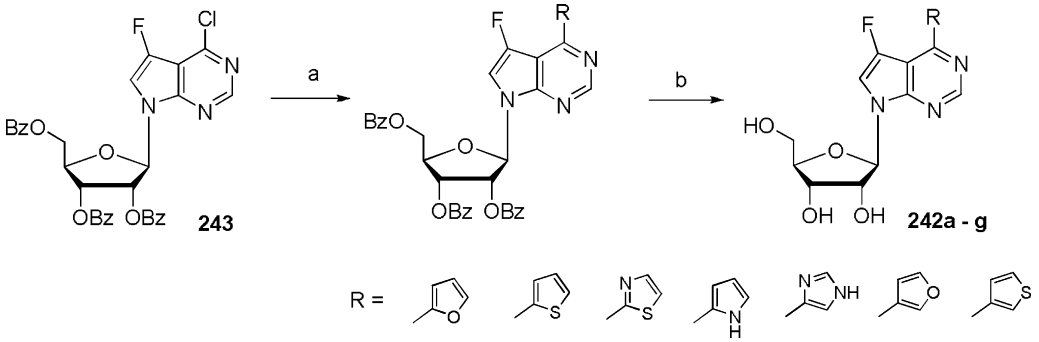
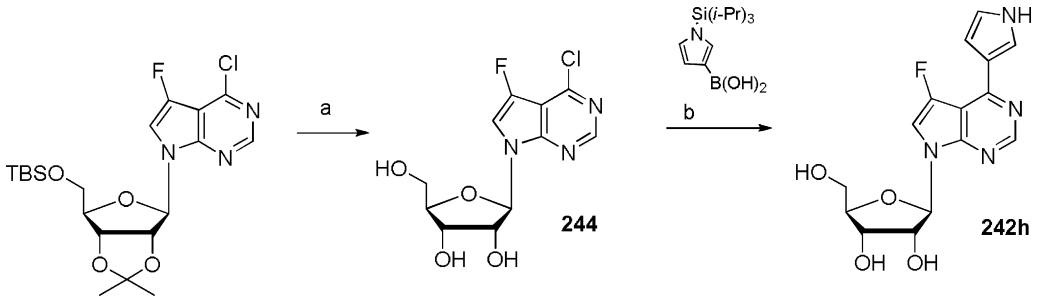


Fig. 13. Modified 7-deazapurine nucleosides.



Scheme 43. Reagents: (a) R-M, Pd cat. and (b) CH_3ONa, CH_3OH.



Scheme 44. Reagents: (a) CF_3CO_2H and (b) $Pd(OAc)_2$, TPPTS, Na_2CO_3, $CH_3CN–H_2O$.

group in position 6 and H, F, or Cl atom in position C-7 [79]. They found that 6-hetaryl-7-fluoro-7-deazapurine ribonucleosides **242** show a significant cytostatic and anti-HCV activity in nanomolar concentrations (Fig. 13). Compounds **242** were prepared either by Pd-catalyzed cross-coupling reactions of the corresponding protected 6-chloro-(7-fluoro)-7-deazapurine ribonucleosides **243** with alkyl- or (het)-arylorganometallics followed by deprotection, or by single step aqueous phase

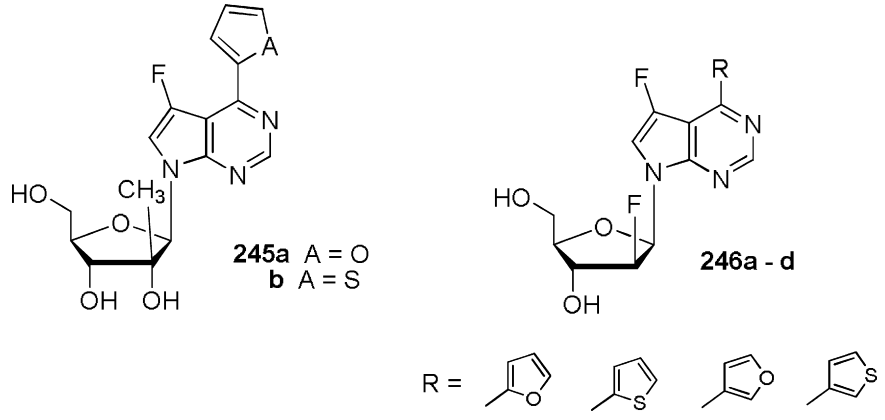
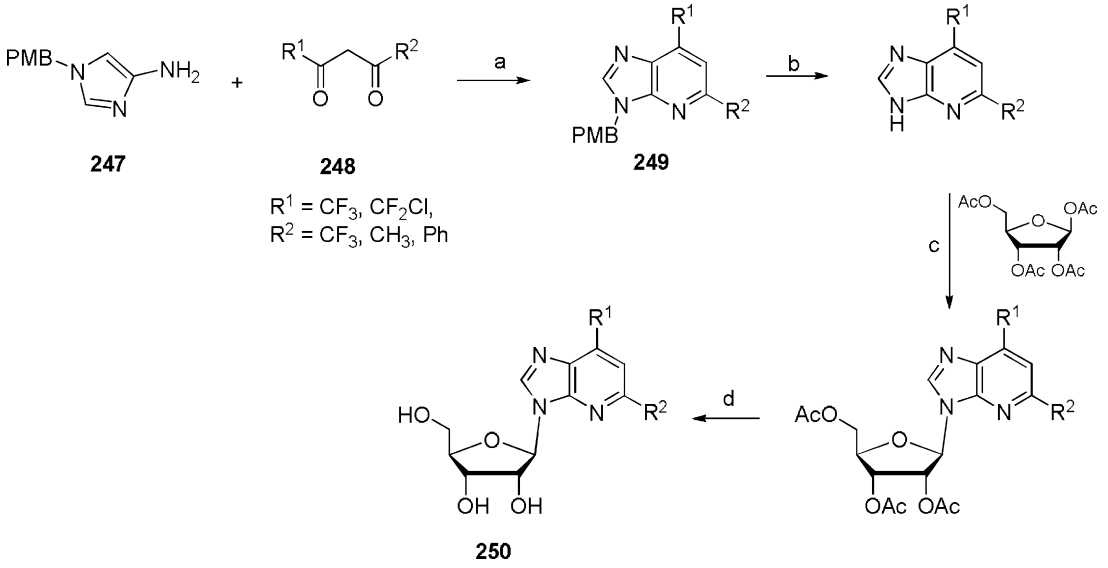


Fig. 14. Modified derivatives of cytostatic 6-hetaryl-deazapurine ribonucleosides.



Scheme 45. Reagents: (a) CH_2Cl_2, reflux, (b) CF_3CO_2H, (c) BSA (O,N-bis(trimethylsilyl)acetamide), TMSOTf and (d) NH_3, CH_3OH.

cross-coupling reactions of unprotected 6-chloro-(7-halogenated)-7-deazapurine ribonucleosides **244** with (het)-arylboronic acids (Schemes 43 and 44).

Hocek and coworkers [80] have also obtained modified derivatives of cytostatic 6-hetaryl-7-deazapurine ribonucleosides: 6-hetaryl-7-fluoro-7-deazapurine 2′-*C*-methyl ribonucleosides **245** and 7-fluoro-6-hetaryl-7-deazapurine 2′-deoxy-2′-fluoroarabinonucleosides **246** (Fig. 14). None of the compounds prepared showed any considerable cytostatic or antiviral activity. It indicates that the cytostatic activity of 6-hetaryl-7-deazapurine nucleosides is only limited to ribonucleosides. Also the introduction of *C*-2′-methyl did not lead to selectivity towards inhibition of RNA-depending RNA polymerase of HCV.

1-Deazapurines (imidazo[4,5-*b*]pyridines) make up an important class of heterocyclic compounds that exhibit a wide range of biological activities and pharmacological properties. Fluorinated 1-deazapurines are phosphodiesterase inhibitors [81] and inhibitors of aurora kinase [82].

The research group of Iaroshenko synthesized a set of fluorinated 1-deazapurines substituted at position C-6 by fluorine-containing groups (Scheme 45) [83,84]. The synthesized scaffolds constitute a platform for the mechanism-based design and synthesis of adenosine deaminase (ADA). Deaminases are of particular interest since many of these enzymes represent drug targets for the design and synthesis of potent drugs for the treatment of various diseases, such as HIV and cancers. The synthesis of 2- and 6-trifluoromethylated 1-deazapurines **249** was performed by formal [3 + 3] cyclization reactions of 5-aminoimidazoles **247** with a set of trifluoromethyl substituted 1,3-dielectrophiles **248**. The corresponding fluorinated nucleosides **250** were synthesized by glycosylation reactions.

Such efforts to design specific inhibitors of deaminases have been focused on molecules that mimic the transition state (TS) structure. Since the TS structure most likely resembles the hydrated intermediate, stable TS mimics containing a hydroxyl group attached to a carbon, located in a position analogous to the purine hydration site, were of interest. The electron-withdrawing trifluoromethyl group facilitates hydration at position C-6 of the purine ring, and that the adducts **A** and **B** might mimic TS of adenosine hydrolytic deamination. Thus 2- and 6-trifluoromethyl containing purines and deazapurines can serve as inhibitors of ADA (Fig. 15).

4. Fluorinated acyclic nucleosides

4.1. Acyclic nucleosides

The interest in acyclic nucleosides began in the mid-1970s when Aciclovir was first reported as a potent anti-herpes drug [85]. Most of the antiviral compounds that are currently used in the treatment of HSV (*herpes simplex virus*), VZV (*varicella zoster virus*) and CMV (*cytomegalovirus*) can be described as acyclic nucleoside analogues. Among these agents, aciclovir and ganciclovir were reported to be efficient antiviral agents with low host toxicity [86,87]. Also penciclovir, a carba analogue of ganciclovir, was found to be more potent and highly selective antiviral agent against HSV and VZV [88] (Fig. 16). This ciclovirs and their analogues have stimulated extensive research in the synthesis of new acyclic analogues mimicking the sugar portion of naturally occurring nucleosides.

The selectivity of these acyclic nucleoside analogues is due, in part, to the fact that they are phosphorylated only in virus-infected

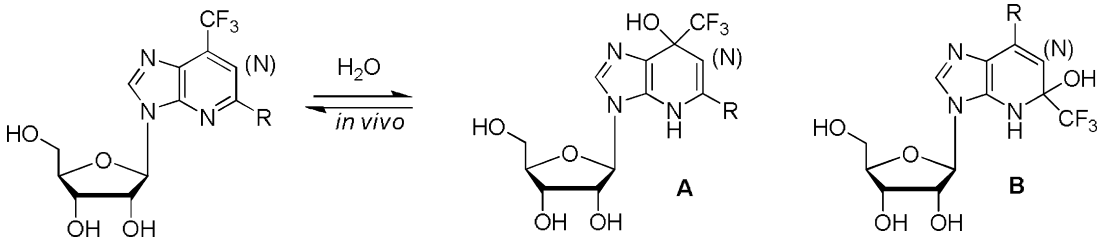


Fig. 15. Trifluoromethyl-containing 1-deazapurines as potent inhibitors of adenosine deaminase.

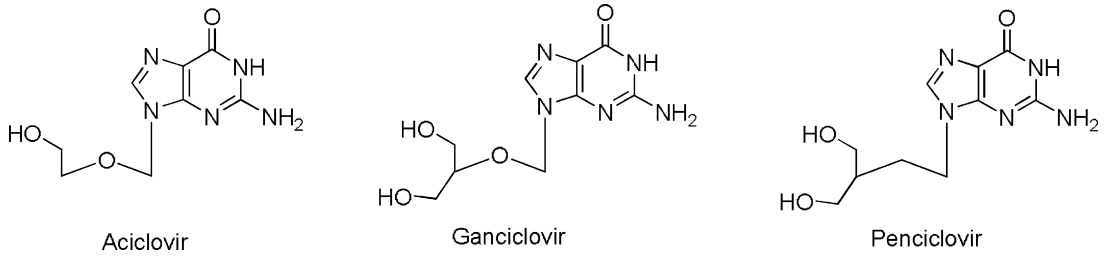


Fig. 16. Structures of aciclovir, ganciclovir and penciclovir.

cells, where a virus specific thymidine kinase of low substrate specificity converts the nucleoside analogues to their monophosphate derivatives [89]. The monophosphates are converted to diphosphates and then to the corresponding triphosphates by cellular enzymes [90]. The triphosphates prevent viral replication by inhibition of the viral DNA polymerase.

Fluoro derivatives of ganciclovir and penciclovir were evaluated as tracers for non-invasive positron emission tomography (PET) imaging of HSV type 1 thymidine kinase (HSV-1 TK) gene expression [91–93]. PET uses short-lived positron-emitting isotopes to trace labelled compounds *in vivo*. The most commonly used isotopes are ^{11}C, ^{18}F, ^{15}O, ^{13}N, ^{76}Br and ^{124}I. The half-life time of fluorine radioisotope ^{18}F is 109 min.

Moreover, in the area of medicinal chemistry, the introduction of fluorine plays a significant role in the development of new drug agents because of improving the metabolic stability or modulating the physicochemical properties or increasing binding affinity to a target protein [94,95].

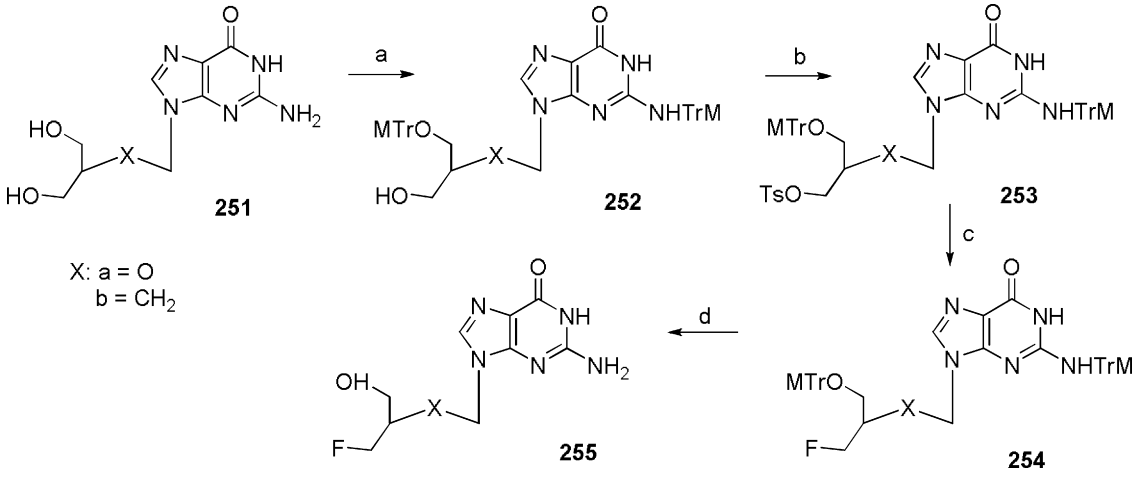
These findings led to the synthesis of a number of analogues of ganciclovir and penciclovir in order to study further effects of structural modifications on antiviral activity. Among these analogues 9-[3-fluoro-1-hydroxy-2-propoxy)methyl]-guanine (FHPG) **255a** was found to be biologically active and phosphorylated by the viral kinase. An efficient and convenient synthesis of ^{18}F labelled FHPG was reported in 1996 by Alauddin et al. [96]. It produced labelled product in amounts and purity suitable for animal and patient studies by positron emission tomography (Scheme 46).

Similar synthesis and preliminary biological evaluation of 9-(4-[^{18}F]-fluoro-3-hydroxymethylbutyl)-guanine [^{18}F]FHBG **255b** was reported in 1998 by Alaudin and Conti [93]. Penciclovir **251b** was converted to 9-[N^2,O-bis-(methoxytrityl)-3-(tosylmethylbuthyl)]-guanine **253b** by treatment with methoxytrityl chloride followed by tosylation. The tosylate was reduced with TBAF or KF to produce the 4-fluoro-N^2-O-bis-(methoxytrityl) derivative **254b**. Removal of the methoxytrityl groups by acidic hydrolysis produced FHBG **255b** (Scheme 46). Radiolabelled product was prepared by fluorination of the tosylate **253b** with [^{18}F]KF. Synthesis time was 90–100 min including HPLC purification with radiochemical purity >99%. *In vitro* studies revealed that [^{18}F]FHBG may be useful for imaging transduced cells for use in imaging of viral infection and gene therapy of cancer.

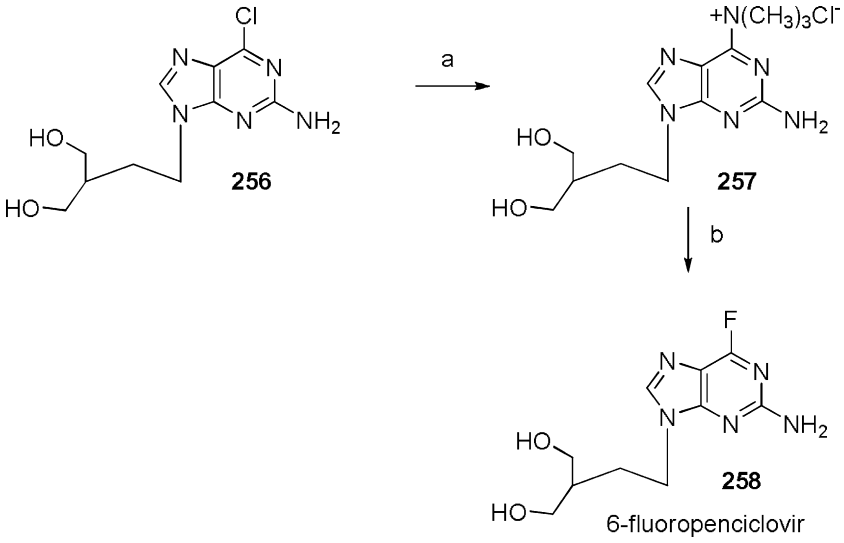
A new convenient and improved synthesis of fluorinated penciclovir analogues 9-(4-fluoro-3-hydroxymethylbutyl)guanine (FHBG) has been described by Yin and coworkers [97]. They obtained also a new type of fluorinated cyclovir, 6-fluorosubstituted penciclovir, 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxy-methylbutyl)purine **258.** The preparation of **258** is shown in Scheme 47. 2-Amino-9-(4-hydroxy-3-hydroxymethyl-butyl)-N,N,N-trimethyl-9H-purin-6-aminium chloride **257** was obtained in the reaction of ethanolic TMA solution and purine **256.** Compound **257** was reacted with KF in DMF to yield the final 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxymethylbutyl) purine **258**.

The exploration of the active site of HSV type-1 thymidine kinase (HSV1-TK) with penciclovir showed that position C-6 of the purine ring was pertinent to activity of penciclovir. 6-Fluoropenciclovir, radiolabelled with ^{18}F was reported more recently as a novel PET probe for imaging HSV1-tk reporter gene expression [98].

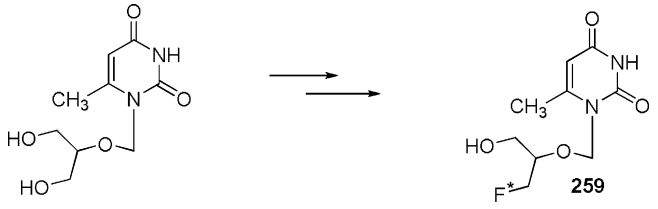
Grote and coworkers have synthesized a group of nucleoside analogues, among them methyl analogues of ganciclovir and penciclovir, their related ^{18}F labelled fluoro compounds and a novel 6-methyl-1-[(1,3-dihydroxy-2-propoxy)-methyl]uracil and its ^{18}F labelled 3-fluoro-derivative **259** [99]. To obtain [^{18}F]-labelled tracers the tosylated and methoxytritylated precursors were radiolabelled with a K[^{18}F]F/Kryptofix 2.2.2 complex in acetonitrile, followed by splitting off the protection groups under acidic conditions (Scheme 48).



Scheme 46. Reagents: (a) MTrCl, (b) TsCl, (c) TBAF or KF and (d) HCl.



Scheme 47. Synthesis of 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxymethyl-butyl) purine **258**. Reagents: (a) TMA, C_2H_5OH and (b) KF, DMF.

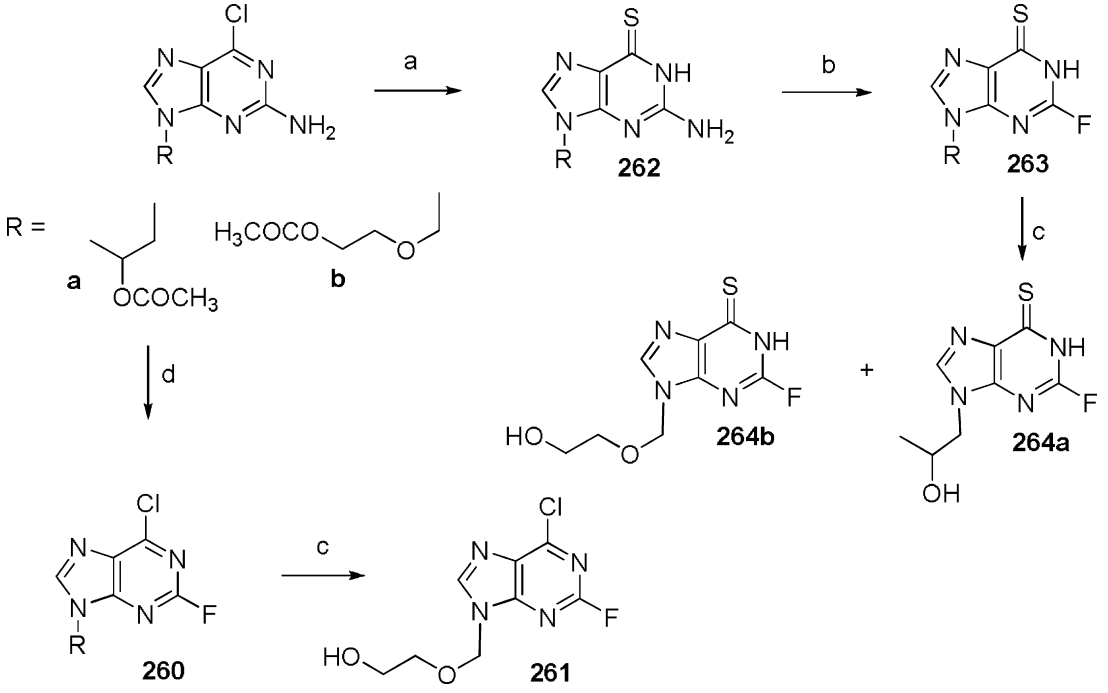


Scheme 48. The 6-methyl-1-[(1,3-dihydroxy-2-propoxy)-methyl]uracil and its ^{18}F labelled 3-fluoro-derivative **259**.

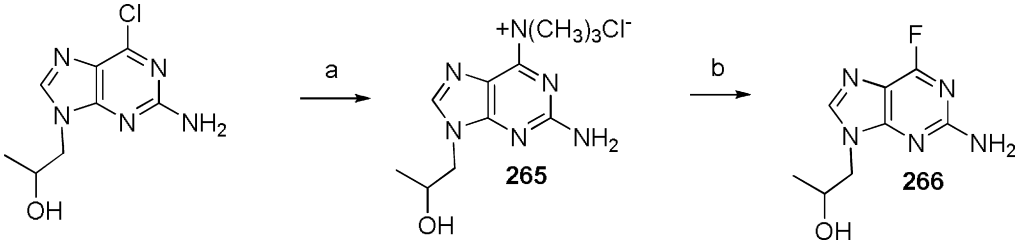
Raic-Malic and her research group [100] synthesized other types of fluorinated acyclic nucleoside analogues containing a 9-(2-hydroxypropyl) side chain (compound **264a**) and a 9-(2-hydroxyethoxymethyl) side chain (compounds **264b** and **261)** by a multistep synthetic route involving Balz–Schiemann's fluorination as a key reaction. Introduction of fluorine in position C-2 of the purine ring in **260a**, **260b**, **263a**, and **263b** was performed using 60% HF/pyridine and *t*-butyl nitrite in nonaqueous media (Scheme 49).

6-Fluoropurine nucleoside analogue **266** was obtained by the nucleophilic replacement of the quaternary ammonium salt **265** as intermediate with potassium fluoride (Scheme 50). New compounds containing a 2-fluoro- and 6-fluoropurine moiety were evaluated for their cytostatic activity.

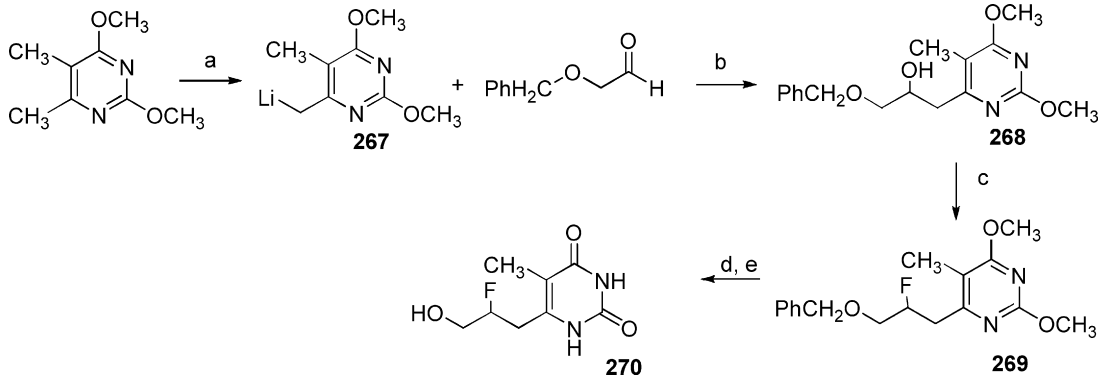
One year later they synthesized a novel fluorinated pyrimidine derivative **270** with 2-fluoro-3-hydroxypropyl side-chain attached to C-6 of the pyrimidine ring. The obtained compound exhibited better binding affinity to HSV-1 TK than aciclovir and ganciclovir [101]. The pyrimidine derivatives containing an acyclic side-chain attached to C-6 of the pyrimidine ring were synthesized according to Scheme 51. The key intermediate, 6-(3-



Scheme 49. Reagents: (a) $(NH_2)_2CS$, C_2H_5OH, (b) 60% HF-pyridine, *t*-$BuNO_2$ and (c) LiOH, $CH_3CN–H_2O$.



Scheme 50. Reagents and conditions: (a) Me_3N, DMF and (b) KF, DMF.



Scheme 51. Reagents: (a) *n*-BuLi, THF, (b) −50 °C, acetic acid, (c) DAST, CH_2Cl_2, (d) AcCl, H_2O and (e) BCl_3, CH_2Cl_2.

benzyloxy-2-hydroxypropyl)-2,4-dimethoxy-5-methylpyrimidine **268** was prepared *via* an addition reaction of the lithiated 2,4-dimethoxy-5, 6-dimethylpyrimidine **267** with benzyloxyacetaldehyde. Compound **269** was obtained by the fluorination of **268** using DAST as the fluorinating reagent. Deprotections of the methoxy groups in **269** and, in the next step the benzyloxy group, were carried out with acetyl chloride and boron trichloride, respectively, to give the target compound **270**.

The same research group [102] obtained a set of nonconventional C-6 fluoroalkylated and fluorophenylalkylated pyrimidine acyclic nucleoside mimetics **271** and **272** as model compounds for development of tracer molecules in PET (Fig. 17) The synthetic route for introduction of a fluoroalkyl, fluoroalkenyl, fluorophenylalkyl, and fluorophenylalkenyl side chain at C-6 of pyrimidine involved the lithiation of pyrimidine and subsequent nucleophilic addition or substitution reactions of the organolithium intermediate. The compounds obtained were evaluated for their antiviral and cytostatic activities. A few from among all C-6 fluorophenylalkylated pyrimidine derivatives showed a slight activity against CMV, VZV, and Coxsackie B4 virus, respectively and showed no cytotoxic effect.

In 2009 they synthesized C-6 fluoroalkylated pyrimidine derivatives **273** and **274** with 3,3,4,4,4-pentafluoro-1-butenyl side chain [103]. It was found that introduction of a double bond gave a slight rigidity to the unsaturated nucleoside analogues [104,105]

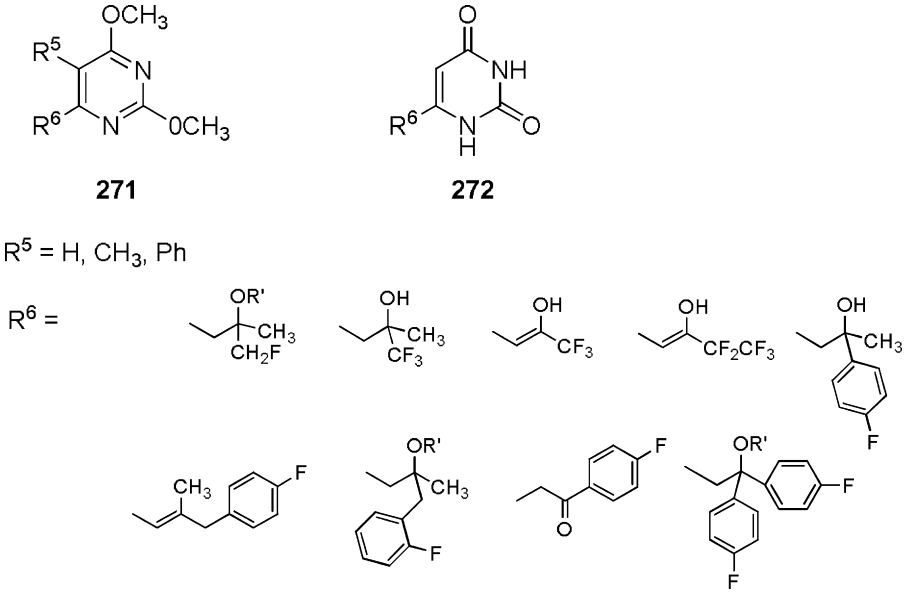
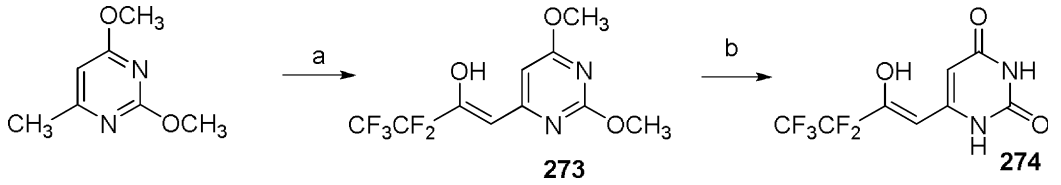


Fig. 17. The C-6 fluoroalkylated and fluorophenylalkylated pyrimidine derivatives **271** and **272**.



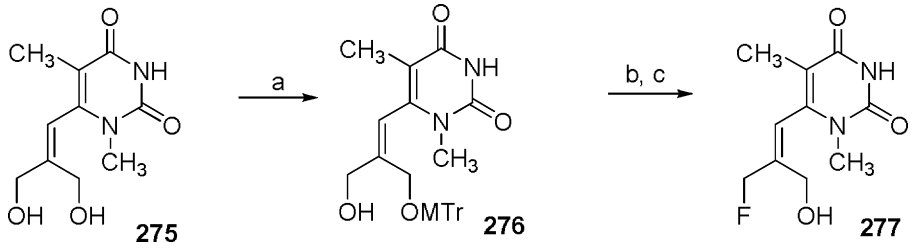
Scheme 52. Reagents: (a) LDA, THF, ethyl pentafluoropropionate and (b) NaI, TMSCl, CH_3CN.

which stabilized these compounds in the best conformation to improve their interactions with phosphorylating enzymes. The substituted fluoroalkenyl 2,4-dimethoxypyrimidine derivative **273** was synthesized by lithiation of 2,4-dimethoxy-6-methylpyrimidine and subsequent reaction of thus obtained organolithium intermediate with ethyl pentafluoropropionate. The novel 2,4-pyrimidinedione, containing 3,3,4,4,4-pentafluoro-1-butenyl side chain (compound **274**) was prepared by demethoxylation of **273** using NaI and TMSCl (Scheme 52).

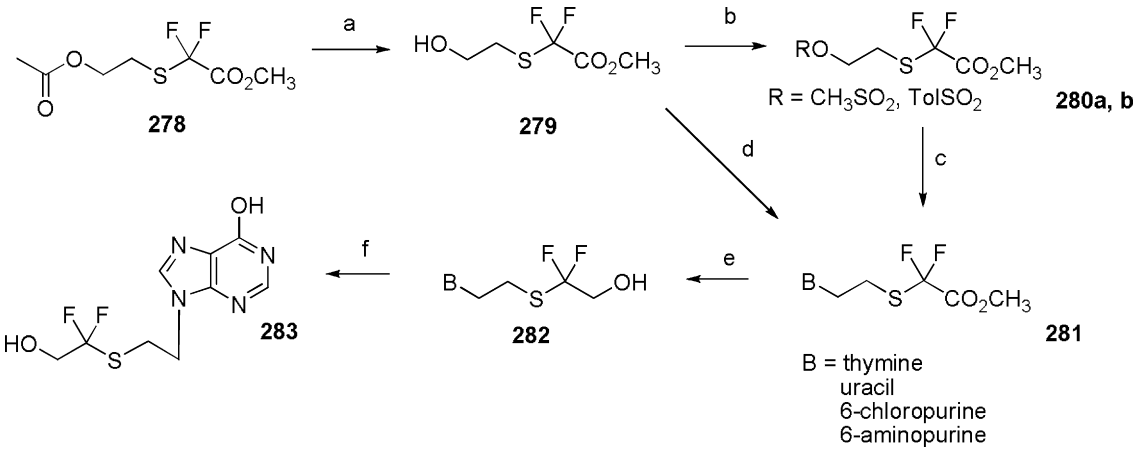
Most recently, in 2011, Raic-Malic and coworkers obtained a new series of conformationally restricted pyrimidine derivatives bearing C-6 isobutenyl side-chain, among them a novel fluoroalkenyl pyrimidine nucleoside mimetic **277** as a model compound for development of tracer molecules in PET [106]. The 6-(1,3-dihydroxyisobutenyl)N-methyl pyrimidine derivative **275** was synthesized according to a multistep procedure. In the next step, one primary hydroxyl group was selectively converted to methoxytritylated group. Thus, the reaction of compound **275** and *p*-anisylchlorodiphenylmethane in the presence of 4-DMAP gave C-6 isobutenyl substituted pyrimidine derivative **276**, as a mixture of *Z*- and (*E*)-isomers in which (*Z*)-isomer prevailed. The treatment of compound **276** with DAST and subsequent hydrolysis, gave monofluorinated compound **277** as a mixture of *Z*- and (*E*)-isomers and a difluorinated derivative as a side product (Scheme 53).

Lequeux has synthesized acyclonucleoside analogues **282** containing a *gem*-difluoromethylene group, in few steps from fluorothioesters [107]. The compounds structurally close to known antiviral agents were tested against a large variety of viruses. The hydrolysis of starting material **278**, obtained in a standard procedure, in the presence of potassium carbonate afforded the expected alcohol **279**. Reaction of the alcohol with the appropriate alkylsulphonyl chloride in the presence of triethylamine and a catalytic amount of DMAP led to products **280a** and **280b**. The alkylation of 6-chloropurine and pyrimidine bases with tosylates **280** gave products **281.** The reduction with sodium borohydride afforded the corresponding alcohols **282**, without any degradation of the nucleic base (Scheme 54).

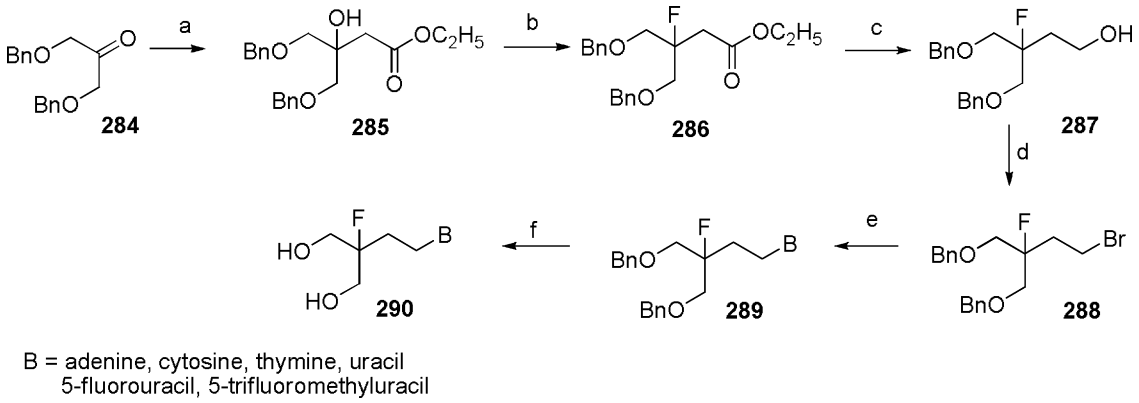
Choi and coworkers have designed and synthesized a series of 3′-fluoropenciclovir analogues **290** with different purine and pyrimidine bases [108]. The strategy for synthesis of 3′-fluoropenciclovir analogues was based on the alkylation of either adenine or pyrimidine bases with bromide **288**. The bromide was prepared from ketone **284** *via* an efficient six-step sequence. A direct reduction of β-fluoroester **286** to the corresponding 3-fluoroalcohol **287** provided an easy entry pathway towards the synthesis of 3′-fluoropenciclovir analogues **290** (Scheme 55). The synthesized 3′-fluoropenciclovir analogues were evaluated for their antiviral activities against the poliovirus, HSV-1, HSV-2 and HIV.



Scheme 53. Synthesis of compound **277**. Reagents: (a) MTrCl, DMAP, DMF, (b) DAST, CH_2Cl_2 and (c) 5% methanolic HCl.



Scheme 54. Reagents: (a) K_2CO_3, CH_3OH, (b) TsCl, Et_3N, DMAP, CH_2Cl_2, (c) 6-chloropurine, NaH, THF, (d) 6-chloropurine, or 6-aminopurine, or N^3-Bz-thymine, or N^3-Bz-uracil, DIAD, PPh_3, THF and (e) $NaBH_4$, C_3H_5OH, (f) for 6-chloropurine: $HSCH_2CH_2OH$, CH_3ONa, CH_3OH.



Scheme 55. Synthesis of 3′-fluoropenciclovir analogues **290**. Reagents: (a) LDA, CH_3CO_2Et, THF, (b) DAST, DCM, (c) $LiAlH_4$, THF, (d) NBS, PPh_3, CH_2Cl_2, (e) base, Cs_2CO_3 and (f) BCl_3, CH_2Cl_2.

4.2. Acyclic nucleoside phosphonates

After the acyclic nucleoside analogues have been taken up by the cells, they have to be phosphorylated through three consecutive phosphorylation steps. Acyclic nucleoside phosphonates (ANPs) are nucleotide analogues with phosphorous atom attached to the side aliphatic chain through a stable P–C bond. In contrast to the phosphate group, a phosphonate group cannot be cleaved off by cellular hydrolases. Since the acyclic nucleoside phosphonates already contain a phosphate-mimetic group, stably attached through P–C bond, they need only two, instead of three, phosphorylation steps to reach the active metabolite stage. ANPs exhibit various antiviral, cytostatic, antiparasitic and immunomodulatory properties. Three ANPs (cidofovir, adefovir and tenofovir) (Fig. 18) are active components of potent antivirals used in human medicine for treatment of hepatitis B, AIDS, and other diseases caused by DNA viruses [109,110].

An interesting subclass of ANPs is represented by the purine N-(3-fluoro-2-(phosphonomethoxy)propyl) (FPMP) derivatives **291** [111–113] (Fig. 18) These derivatives exhibit potent and selective activity against retroviruses (HIV-1 and HIV-2) [114].

In 1993 Jindrich and his group [115] prepared N-(3-fluoro-2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases which exhibited a significant selective activity against a broad spectrum of retroviruses. They obtained racemic N-(3-fluoro-2-phosphonomethoxypropyl) derivatives of adenine, guanine, cytosine and 3-deazaadenine (compounds **295**). The compounds were prepared from the corresponding N-(3-fluoro-2-phosphonomethoxypropyl) derivatives after protection of amino group at the heterocyclic ring by selective benzoylation, reaction with diisopropyl-*p*-toluenesulphonyl oxymethyl phosphonate and subsequent removal of the protecting groups (Scheme 56). Chiral FPMP derivatives were prepared in the reaction of heterocyclic base with the corresponding chiral synthons, followed by deprotection.

Compared to the original laborious procedure, an efficient method for the synthesis of N^9-[3-fluoro-2-(phosphonomethoxy)propyl] (FPMP) derivatives of purine bases was developed in 2011 by Janeba and coworkers [116]. Both (R)- and (S)-enantiomers of the N-6 substituted FPMP derivatives of adenine and 2,6-diaminopurine were prepared and their anti-HIV and anti-Moloney *murine sarcoma virus* (MSV) activity was evaluated.

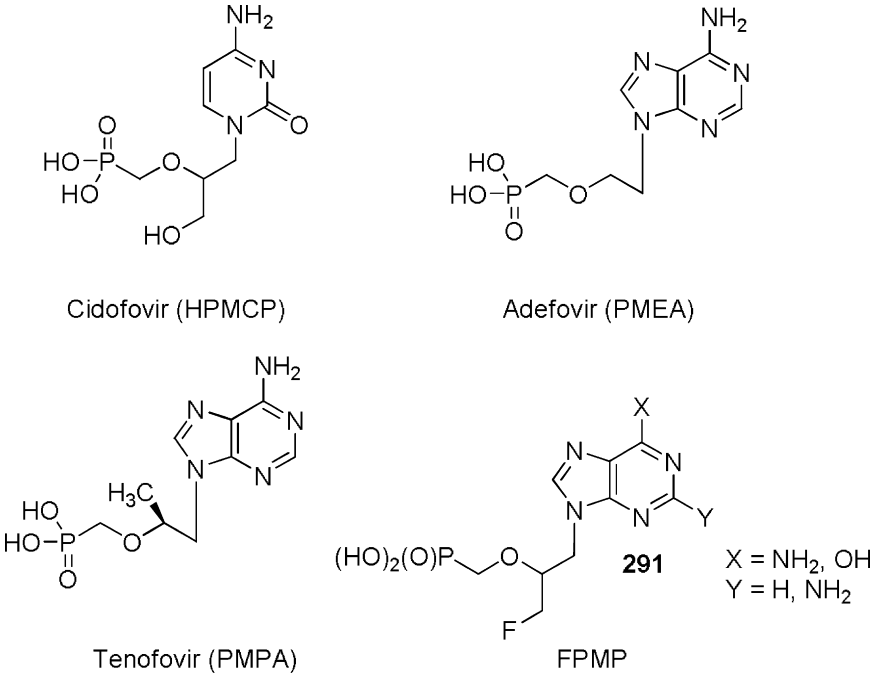
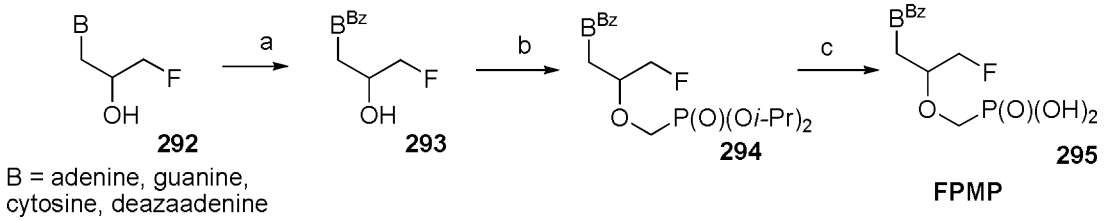


Fig. 18. Antiviral acyclic nucleoside phosphonates.



Scheme 56. Synthesis of FPMP **295**. Reagents: (a) i. TMSCl, pyridine, ii. BnCl, iii. NH_4OH, (b) i. $CH_3C_6H_4$-$SO_2OCH_2P(O)(Oi\text{-}Pr)_2$, NaH, DMF, ii. CH_3ONa, CH_3OH and (c) TMSBr, CH_3CN.

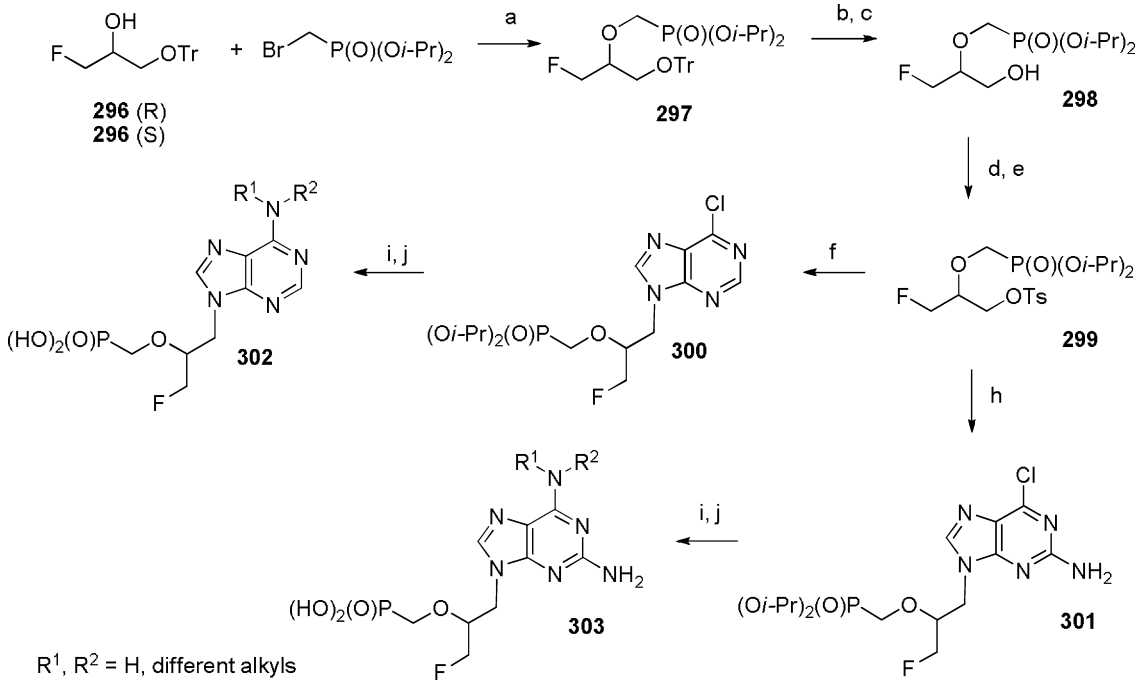
Enantiomeric 3-fluoro-1,2-propanediols were used in the original synthesis of the FPMP derivatives. Diols were converted regioselectively to the corresponding fluorohydrines **296**. Alkylation of the fluorohydrines afforded phosphonates **297**. Detritylation of compounds **297** gave acceptable yields of the derivatives **298**. Both enantiomers were tosylated and gave the desired alkylating agents **299**. Compounds **300** were prepared by condensation of the sodium salt of 6-chloropurine with the corresponding alkylating agents **299**. Condensation of the sodium salt of 2-amino-6-chloropurine with the tosylates **299** afforded the desired products **301**. Heating of 6-chloropurine intermediates **300** and **301** with the appropriate alkylamine or dialkylamine followed by the standard removal of the isopropyl ester groups with TMSBr afforded the products **302** and **303** (Scheme 57).

Chen and coworkers [117] obtained novel α-fluoroderivatives of PME and HPMP **307**, **308** and **311** by coupling of derivatives **305** and **310** with the corresponding purine and pyrimidine nucleic bases under either modified Mitsunobu conditions or base catalyzed alkylation conditions. Treatment of the diesters **306** with concentrated ammonia led to the formation of FPMEA **307** and the corresponding salts of monoethyl phosphonates **308** (Scheme 58). The synthesized fluorinated acyclic nucleoside phosphonates were tested against a broad spectrum of viruses.

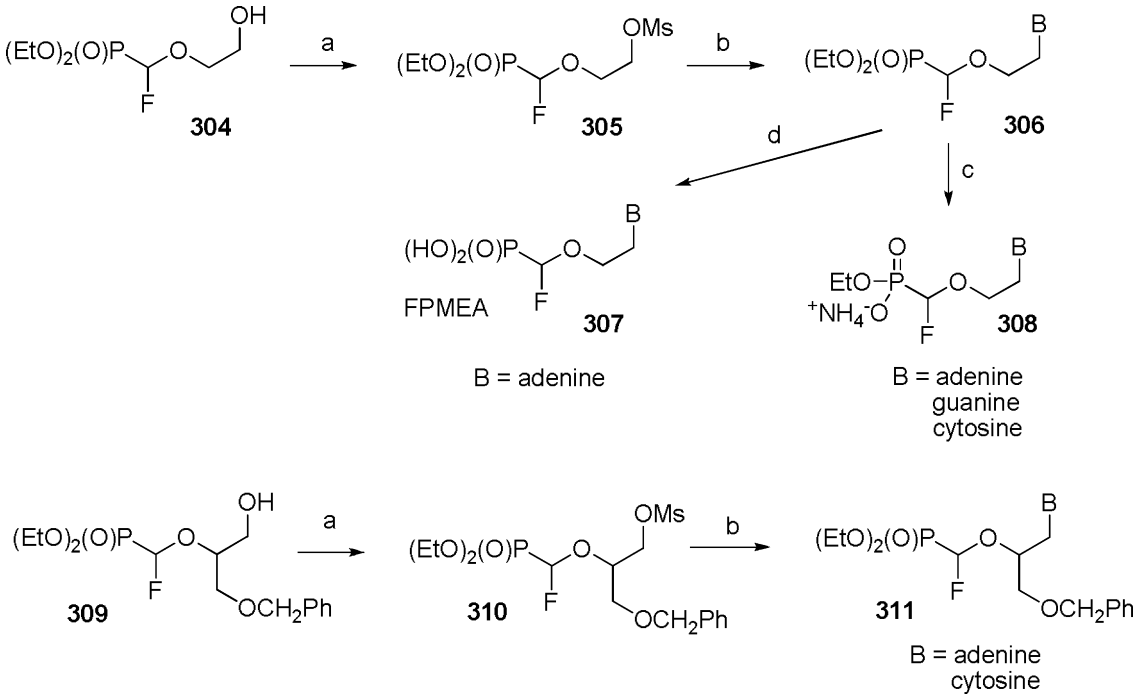
Pomeisl and his research group [118] developed a new group of potent inhibitors of thymidine phosphorylase based on the structure of modified and metabolically stable pyrimidine ANPs. They investigated in particular the novel synthesis of fluorinated derivatives containing trifluoromethyl group in the side chain such as 5-ethyl-1-[3,3,3-trifluoro-2-(phosphonomethoxy)propyl]uracil and thymine derivatives **313**. Trifluoromethyloxirane was found to be an excellent key reagent for the introduction of 1,1,1 trifluoropropan-2-ol moiety. The reaction of (trifluoromethyl)oxirane with 4-methoxypyrimidin-2-one in the presence of cesium carbonate afforded hydroxyl derivatives **312**, which were further alkylated with (diisopropoxyphosphoryl)methyl tosylate in the presence of sodium hydride. Finally, the phosphonates were deprotected by treatment with TMSBr followed by hydrolysis to give compounds **313** (Scheme 59).

Jansa et al. [119] have described very recently a similar procedure for the preparation of several acyclic nucleosides and acyclic nucleoside phosphonates substituted at the C-2′ position of the aliphatic part by the trifluoromethyl group. The reaction of 1,1,1-trifluoropropan-2-ols **314** with the reagent for the introduction of the methylphosphonic residue afforded the desired phosphonates. Various purine (((1,1,1-trifluoropropan-2-yl)oxy)-methyl)phosphonic acids **315** were prepared as CF_3- analogues of tenofovir (Scheme 60).

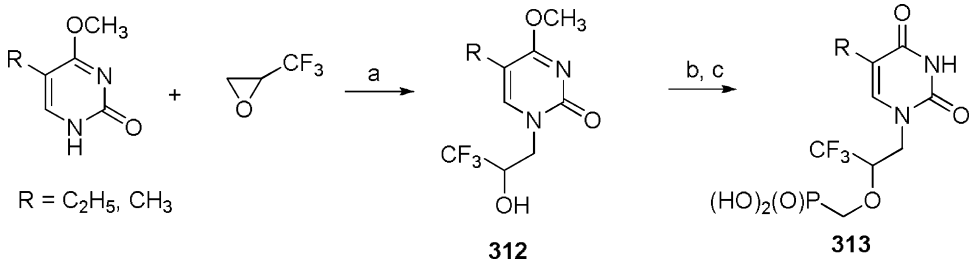
The ability of synthesized compounds **315** to inhibit the bacterial toxin was tested in cell-based *in vitro* model. Unfortunately, none of the prepared compounds exhibited any promising biological properties in the assays tested.



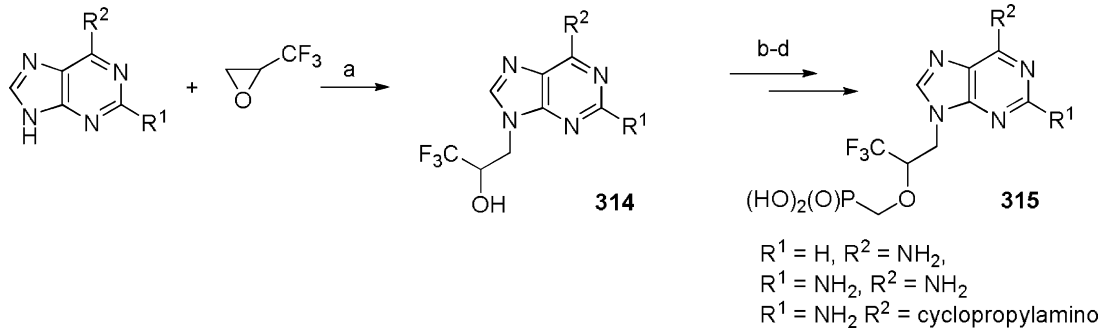
Scheme 57. Reagents: (a) NaH, DMF, (b) CH_3CO_2H, (c) Dowex D50 W A8 (H^+ form), aq. MeOH, (d) TsCl, Et_3N, CH_2Cl_2, (e) TsCl, pyrimidine, DMAP, (f) 6-chloropurine, NaH, DMF, (h) 2-amino-6-chloropurine, NaH, DMF, (i) amine, CH_3CN and (j) TMSBr, CH_3CN.



Scheme 58. Reagents: MsCl, Et_3N, CH_2Cl_2, (b) base, Cs_2CO_3, DMF, (c) aq. NH_3 and (d) TMSBr, CH_2Cl_2.



Scheme 59. Reagents: (a) Cs_2CO_3, DMF, (b) $TsOCH_2P(O)(Oi\text{-}Pr)_2$, NaH, THF and (c) TMSBr, CH_3CN.



Scheme 60. Reagents: (a) Cs_2CO_3, DMF, (b) NH_3, C_2H_5OH or cyclopropylamine, CH_3CN, (c) $BrCH_2P(O)(Oi\text{-}Pr)_2$, NaH, DMF and (d) TMSBr, CH_3CN.

5. Fluoroalkenyl derivatives of nucleosides and nucleobases

Fluoroalkenyl nucleobases and their analogues are particularly attractive in regard of their potent biological activities. It has been shown that pyrimidine [120,121] as well as purine [122–124] derivatives having unsaturated carbon substituents attached to the ring show significant cytostatic and antiviral activity. C-5 and C-6 Alkenyl substituted pyrimidines as well as C-2, C-6 and C-8 alkenyl substituted purines have been synthesized by the palladium catalyzed Stille and Heck cross coupling reactions [125]. In particular, 5-halogenovinyluracils and their nucleoside analogues are characterized by significant and selective biological activities. (*E*)-5-(2-Bromovinyl)uracil (BVU) and (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) (Fig. 19) are effective antiviral agents for *herpes simplex virus* type 1 and against *varicella zoster virus* [126,127]. On the other hand, the second isomer of BVDU, (*Z*)-5-(2-bromovinyl)-2′-deoxyuridine has only a very low activity, thus showing the critical effect of the configuration around the double bond.

The first approach to synthesize 5-(fluoroalkenyl)uracils and their 2′-deoxyribonucleosides was taken in 1982 by Coe and coworkers [128]. They synthesized 5-(2,2-dichloro-1-fluorovinyl)-2,4-dimethoxypyrimidines **317**, and 5-(perfluoropropen-1-yl)-2,4-dimethoxypyrimidines as a mixture of *E* and *Z* isomers **318**

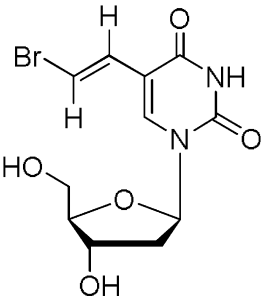


Fig. 19. BVDU as a selective inhibitory agent for HSV-1.

and **319**. Demethylation of **317** gave 5-(2,2-dichloro-1-fluorovinyl)uracil **320** and demethylation of mixture of **318** and **319** gave some pure (*E*)-5-(perfluoropropen-l-yl)uracil **321**. The syntheses were carried out on 5-lithio-2,4-dimethoxypyrimidine **316** which was obtained by the action of butyllithium on 5-bromo-2,4-dimethoxypyrimidine. Reaction of **316** with 1,1-dichlorodifluoroethene afforded 5-(2,2-dichloro-1-fluorovinyl)-2,4-dimethoxypyrimidine **317**. In a similar way, **316** was reacted with perfluoropropene to give a mixture of *E*- and (*Z*)-5-(perfluoropropen-1-yl)-2,4-dimethoxypyrimidine **318** and **319**. Removal of methyl groups was accomplished by the use of sodium iodide in acetic acid to give 5-substituted uracils which were converted into 2′-deoxyribonucleosides **322** by standard procedures to give a mixture of β and α anomers. Compound **324** was obtained from lithio compound **323** as a mixture of *Z* and *E* isomers (Scheme 61).

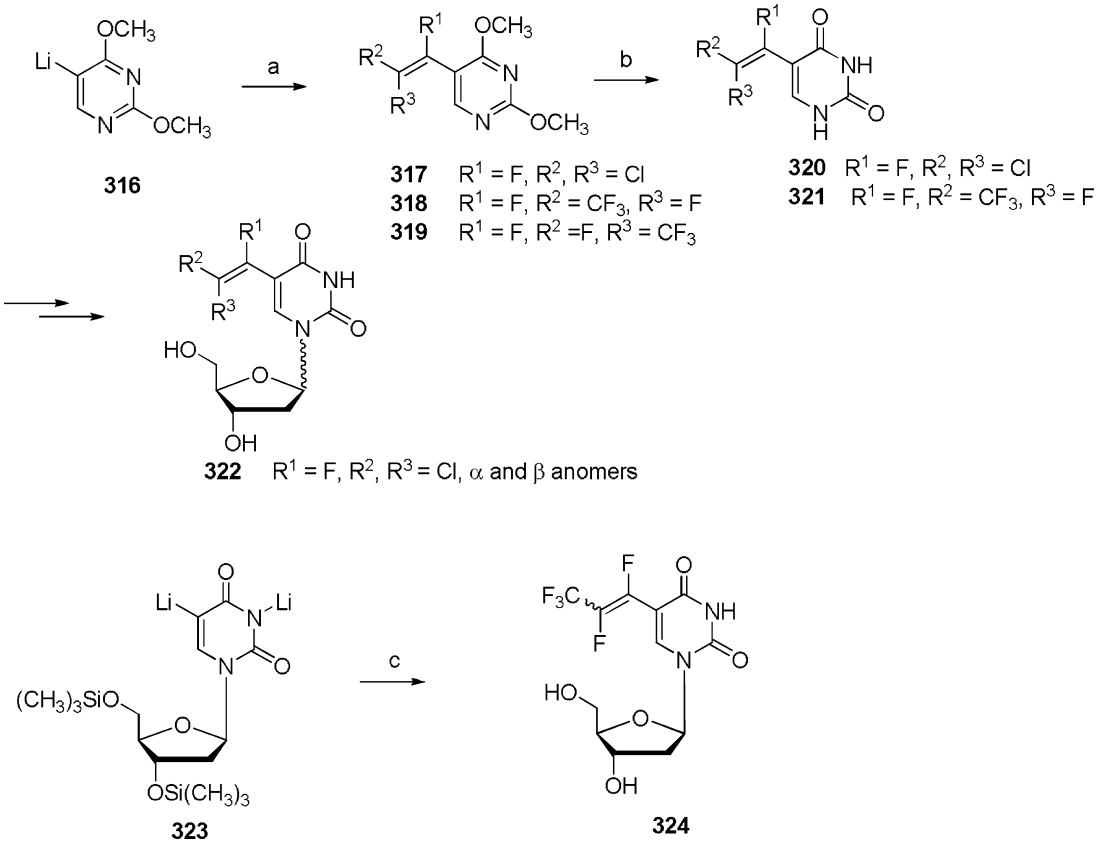
The 5-substituted 2′-deoxyuridines **322**, and **324** were tested for antiviral activity against various strains of *herpes simplex virus*, type 1. Compound **322** showed significant activity, whereas the other compounds were inactive.

Wójtowicz-Rajchel et al. [129] obtained in 2006 various pentafluoropropenyl derivatives of pyrimidine bases substituted at C-5 and C-6 (compounds **326** and **329**). The procedure involved the reaction of appropriate lithium derivatives prepared from both electron-rich **325** and electron-poor **328** pyrimidines, with the hexafluoropropene at a low temperature, *via* an addition-elimination process. A standard workup gave pentafluoropropenyl products as mixtures of *E* and *Z* isomers (Scheme 62).

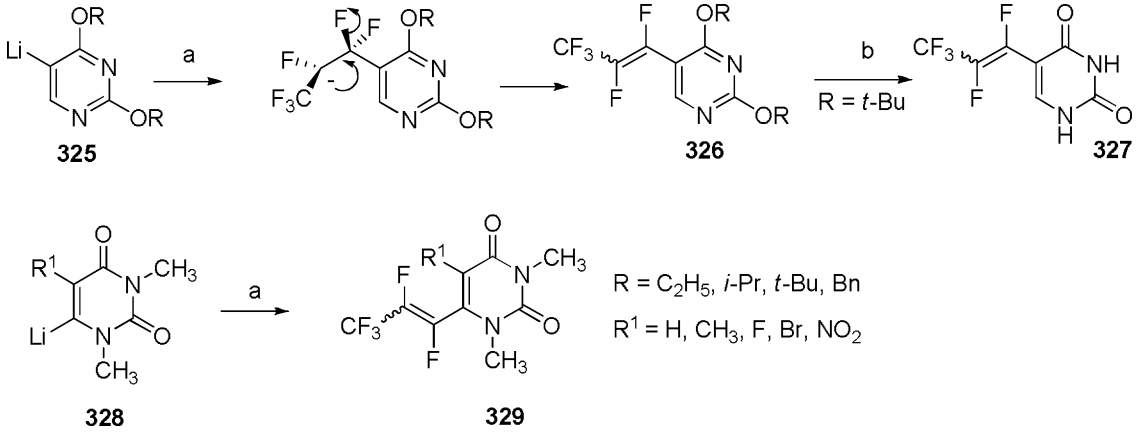
The *E* and *Z* isomers of all synthesized pyrimidines were not separable, but pentafluoropropenyl stereoisomers were easily differentiated by ^{19}F NMR spectroscopy. Both benzyl and *t*-butyl derivatives **326** can be simply converted into a fluorinated derivative of C-5 substituted uracil. In particular, acidic deprotection of *t*-butyl derivative **326** occurred easily under mild conditions to give almost quantitatively 5-perfluoropropen-1-yl uracil **327**.

Interestingly, they observed a significant competing reaction of the organolithium derived from **328b**. Compound **329b** arises from the typical addition-elimination route. The second product **330** found was a result of C-6-C′-6 dimerization, *via* the nucleophilic addition of the organolithium to the C-6 centre of a second molecule of pyrimidine to give an intermediate enolate which then undergoes an addition–elimination process with HFP. The reaction of the precursory enolate with HFP shows total stereoselectivity and that stereoisomer *E* was obtained exclusively. A detailed analysis of ^{19}F NMR spectra showed moreover that **330** was a mixture of diastereoisomers **330a** and **330b** which showed small differences in chemical shifts (Scheme 63).

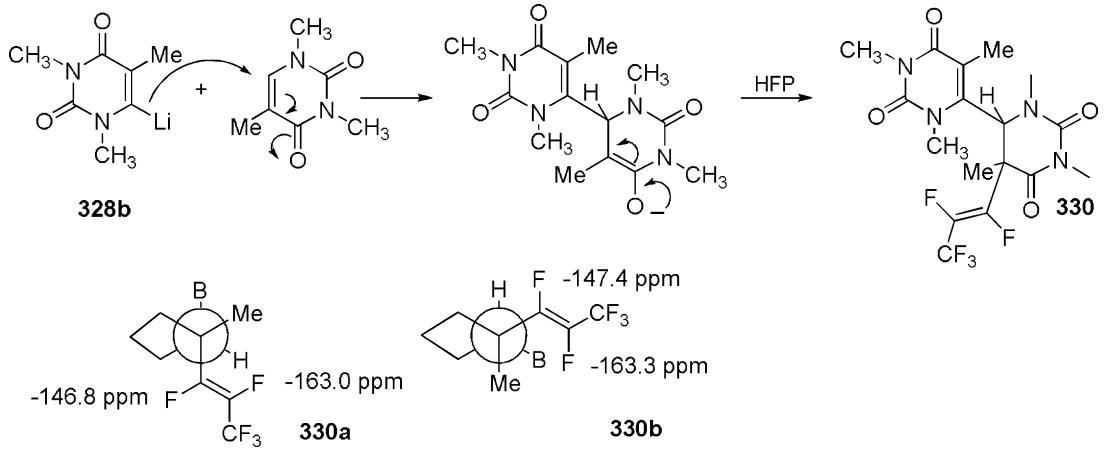
Fluorinated organometallic reagents are very useful synthetic intermediates for introducing a fluorinated unit into organic molecules. Particularly the palladium catalyzed cross couplings of thermally stable perfluoroalkenyl zinc reagents with aryl iodides in



Scheme 61. Reagents (a) CF_2CCl_2 or HFP (hexafluoropropene), Et_2O, (b) NaI, AcOH and (c) HFP, Et_2O.



Scheme 62. Reagents: (a) HFP, THF and (b) CH_3OH, HCl, Et_2O.

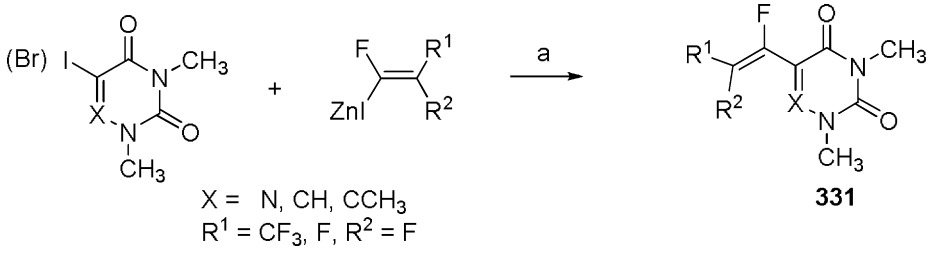


Scheme 63. Proposed mechanism of dimerization of compound **328b** and simplified structures of diastereoisomers **330a** and **330b**.

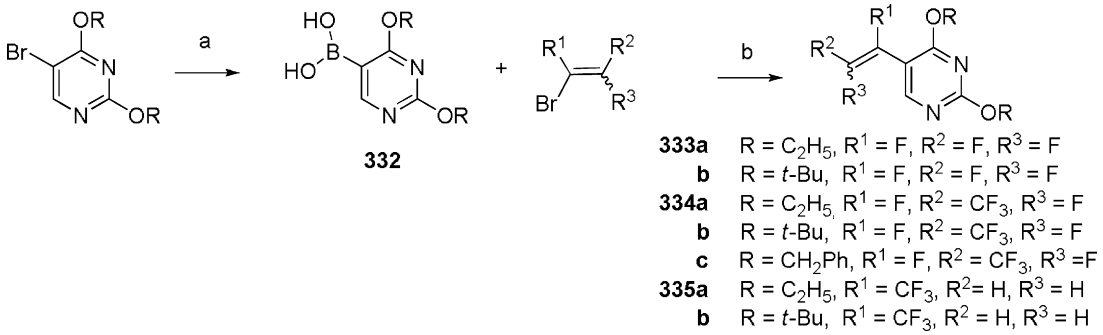
Negishi reactions are very convenient and useful tool in the synthesis of arylperfluoroalkenes. Koroniak and coworkers used a general procedure for palladium(0) catalysed coupling of organometallic, unsaturated fragments with aromatic species, to develop a convenient method for the preparation of 5-perfluoroalkenyl-substituted uracils [130,131]. 1,3-Dimethyl-5-iodouracil and 1,3-dimethyl-5-bromo-6-azauracil reacted smoothly with perfluoroalkenylzinc iodides in the presence of $Pd(PPh_3)_4$ catalyst resulting in the formation of the derivatives **331** as potential synthons of appropriate nucleoside analogues (Scheme 64).

Unfortunately, the organozinc method is characterised sometimes by unsatisfactory yields, while the lithiated pyrimidines only react with HFP, which is a strongly activated electrophile due to the electron withdrawing CF_3 group. Wójtowicz-Rajchel and Koroniak described very recently the synthesis of 5-fluoroalkenyl derivatives of pyrimidines *via* Suzuki–Miyaura coupling reactions [132]. Couplings of 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)-pyrimidines **332** with the appropriate olefins in the presence of $Pd(PPh_3)_4$ and KOH took place smoothly in THF at 65–70 °C to give compounds **333–335** but in unsatisfactory yields. The use of $AsPh_3$ as an external ligand has considerably improved the yield of this reaction, so the catalytic system $Pd(PPh_3)_4/AsPh_3$ was assumed particularly beneficial and was used in transformations of this type (Scheme 65).

Novel purine nucleosides functionalized at position 2 was prepared by Nair et al. [133]. They obtained 2-(2-fluorovinyl) purine ribonucleoside **337** in the Wittig-type olefination procedure as a target molecule designed as a potential inhibitor of the enzyme, inosine monophosphate dehydrogenase (IMPDH). The 2-(2-fluorovinyl) analogue was designed to increase the electrophilic character of the double bond of 2-vinylinosine for enhanced nucleophilic addition of the sulphhydryl group of Cys-331 of



Scheme 64. Synthesis of 5-perfluoroalkenyl derivatives **331** in Negishi reactions. Reagents: (a) $Pd(PPh_3)_4$, DMF.

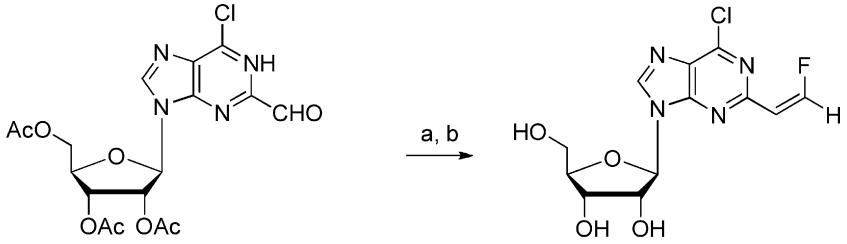


Scheme 65. Suzuki-Miyaura coupling reactions between fluoroalkenes and 5-(dihydroxyboryl)-2,4-*bis*(alkoxy)-pyrimidines **332**. Reagents: (a) i. *n*-BuLi, $B(OC_2H_5)_3$, THF, ii. 0.25 M HCl and (b) $Pd(PPh_3)_4$, $AsPh_3$, THF, 2 M KOH.

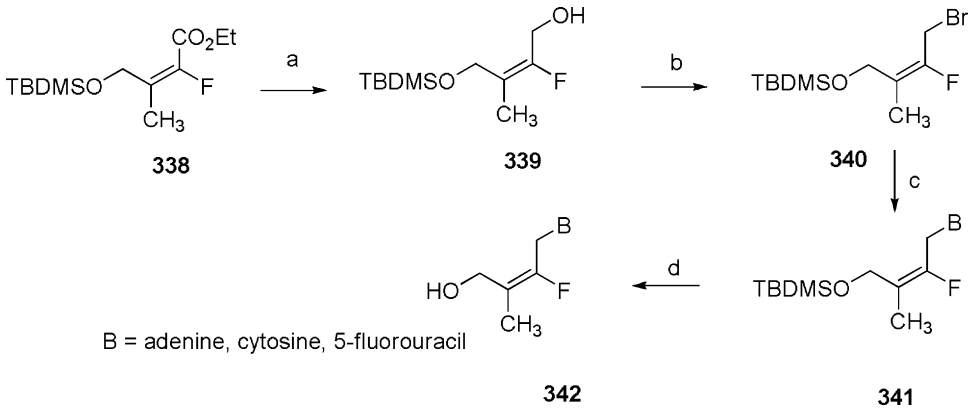
IMPDH at the fluorovinyl group. In the synthetic method, a monofluorinated ylid generated from the reaction of excess tributylphosphine and trichlorofluoromethane, was treated with aldehyde **336** and the vinylphosphonium salt produced was hydrolyzed with aqueous NaOH to give a target molecule **337**. Only (*Z*)-isomer of C-2 substituted nucleoside was isolated (Scheme 66).

Shen and Hong synthesized (*E*)-fluorovinylnucleosides as acyclic analogues of neplanocin A and fluoroneplanocin A, designed as irreversible inhibitors of S-adenosylhomocysteine hydrolase (SAH) [134]. Neplanocin A (Fig. 2) has antitumour activity against mouse leukaemia L1210 cells and broad-spectrum antiviral activity [135]. The general synthetic pathway of synthesis of (*E*)-fluorovinyl nucleosides is given in Schemes 67 and 68. Reduction of ester **338** with DIBAL-H gave alcohol **339**. The conversion of the allylic alcohol to the bromo derivative **340** was accomplished by addition of NBS to a solution of the alcohol and triphenylphosphine. The condensation of bromide **340** with nucleoside bases and the deprotection afforded the desired acyclic fluorovinyl nucleosides. The synthesized compounds **342** were evaluated for their antiviral activity. Compound **343**, which exhibited anti-HIV-1 activity, was also prepared by condensation reaction of 2-amino-6-chloropurine with the bromide **340** followed by deprotection reaction and conversion of 2-amino-6-chloropurine to guanine acyclic nucleoside.

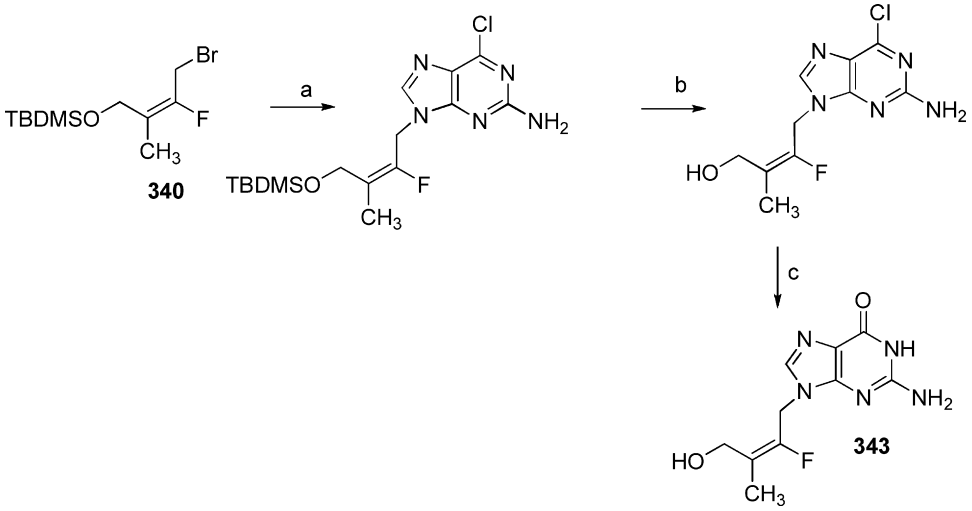
Sigurdsson obtained *via* a direct alkylation the 2′-deoxy-N^3-(3,3,3-trifluoro-propen-1-yl)uridine **344**, an enamine containing trifluoromethyl group in the external unsaturated part of moiety [136]. Generally, the 3,3,3-trifluoropropenyl group ($CF_3CH{=}CH{-}$) has been used to improve the properties of candidate compounds for medicines or agricultural chemicals [137]. Reaction of 3,3,3-trifluoropropyne with 2′-deoxy-5-iodouridine under conditions that have previously been used to prepare 5-alkynyl-2′-deoxyuridine derivatives gave only 2′-deoxy-N^3-(3,3,3-trifluoro-propen-1-yl) uridine **344** (Scheme 69). The mechanism of *N* alkylation in formation of **344** was analogous to the Michael reaction, where the pyrimidine N^3 adds as a nucleophile to the terminal carbon of the alkyne, which is electrophilic due to the presence of the strongly electron withdrawing CF_3 group.



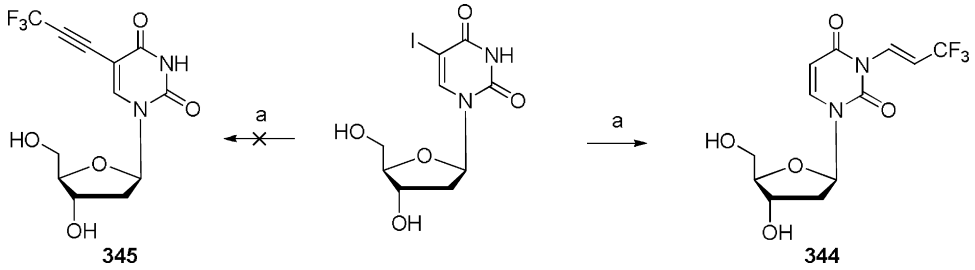
Scheme 66. Reagents: (a) i. Bu_3P, $CFCl_3$, CH_2Cl_2, ii. 10% NaOH and (b) NH_3, CH_3OH.



Scheme 67. Synthesis of (*E*)-fluorovinyl nucleosides **342**. Reagents: (a) DIBAL-H, CH_2Cl_2, (b) NBS, PPh_3, CH_2Cl_2, (c) bases, Cs_2CO_3, DMF and (d) TBAF, THF.



Scheme 68. Synthesis of (*E*)-fluorovinyl guanine nucleoside **343**. Reagents: (a) 2-amino-6-chloropurine, NaH, DMF, (b) TBAF, THF and (c) i. $HSCH_2CH_2OH$, CH_3ONa, CH_3OH, ii. AcOH.

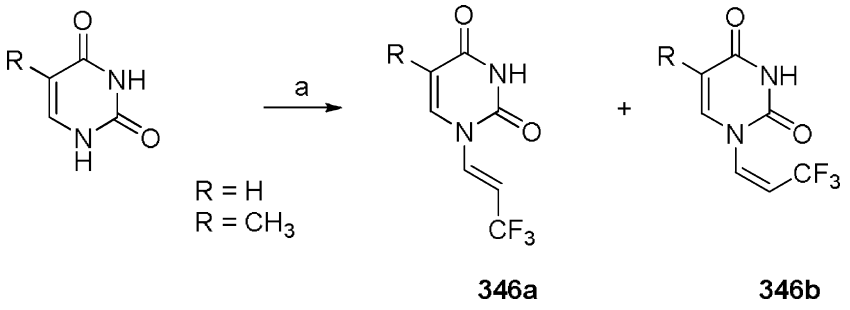


Scheme 69. Reagents: (a) $HCCCF_3$, $Pd(PPh_3)_4$, CuI.

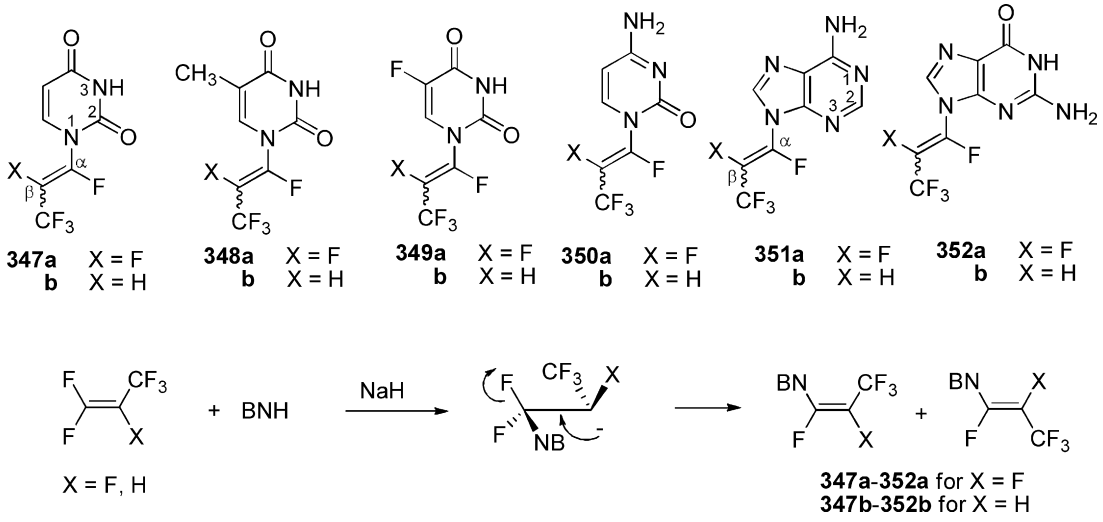
Jiang et al. [138] obtained trifluoromethyl enamines of uracil and thymine **346** from 2-bromo-3,3,3-trifluoropropene, pyrimidynic bases and potassium *t*-butoxide in one pot reaction *via* Michael addition and elimination processes (Scheme 70).

In 2008 Wójtowicz and Koroniak prepared stable α-fluoroenamines of nucleobases [139]. All known α-fluoroenamines readily react with water to give the corresponding amides and hydrogen fluoride in an addition–elimination process [140]. The compounds obtained, however, were absolutely stable and did not undergo hydrolysis on contact with water. The treatment of a whole set of nucleic acid bases and related derivatives with electron-deficient and highly susceptible to nucleophilic attack hexafluoropropene (HFP) or 1,1,3,3,3-pentafluoropropene (PFP) in the presence of sodium hydride gave the corresponding fluorinated N-α,β-difluoro-β-trifluoromethyl and N-α-fluoro-β-trifluoromethyl enamines (Scheme 71). This fluoroalkylation was a result of a Michael type addition–elimination process and gave the desired products **347a**–**352a** and **347b**–**352b** generally in good yields as *E*/*Z* mixtures. In literature nonfluorinated enamines of nucleic acid bases have been obtained in low-yielding, multi-step procedures, and only recently effective methods for the synthesis of N-vinyl derivatives of all nucleic acid bases have been developed [141]. Compounds **347**–**352** were obtained with high regioselectivity for N-9 in the purine case and N-1 in that of pyrimidines. The nucleophilic substitution was also regioselective towards olefin and takes place exclusively at CF_2= (the most positive site) and not at =$CFCF_3$ or =$CHCF_3$. In the carbanion transition state the negative charge is localized on the carbon atom, strongly stabilized by the CF_3 group, and the elimination of the fluoride ion leads to the unsaturated system and consequently in this addition-elimination sequence to the enamine.

The spectroscopic and chemical experimental results demonstrated, that both, (*Z*)-N-α-fluoro-β-trifluoromethyl enamines and obtained recently, in the reaction with 1,2,3,3,3-pentafluoropropene,



Scheme 70. Preparation of β-trifluoromethyl enamines **346**. Reagents: (a) $CF_3C(Br)CH_2$, *t*-BuOK, DMSO.



Scheme 71. Addition–elimination reactions of PNH with HFP and PFP, where BNH is the appropriate pyrimidine or purine with endocyclic N-1 for pyrimidines and endocyclic N-9 for purines.

isostructural (*Z*)-N-β-fluoro-β-trifluoromethyl enamines of nucleobases **347c**–**351c**, in contrast to their *E* analogues, are involved in stereospecific intramolecular interactions [142]. The formation of C^{β}–H···O=C^{2} and C^{β}–H···N^{3} hydrogen bonds helps anchor the planar orientation in stereoisomers *Z*. The flat structure is stabilized in nonpolar solvents. Solvents like DMSO, with high hydrogen bonding abilities, disrupt the intramolecular hydrogen bond and weaken the p–π conjugation of the tetrafluoropropenyl group and the purine or pyrimidine ring. Such interactions of a weak hydrogen bond type essentially affect both ^{19}F NMR and ^{1}H NMR parameters of all *Z* stereoisomers. Additionally the treatment of N-α-fluoro-β-trifluoromethyl enamine of uracil **347b** with *t*-BuLi and subsequently with deuterated methanol gave different results for *E* and *Z* stereoisomers (Scheme 72).

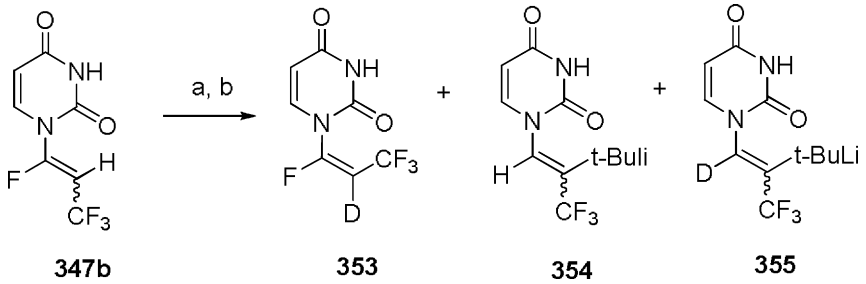
The *E* stereoisomer, with the C^{β}–H proton not involved in the hydrogen bond, reacted as expected, so as a result of proton abstraction it gave a lithiated derivative that was quenched by CD_3OD to give compound **353**, with the preserved double bond configuration. In the *Z* stereoisomer in which the proton was engaged in an interaction with the carbonyl group, *t*-BuLi behave as a typical nucleophile giving a mixture of addition–elimination products **354** and **355** as a result of the reaction with CD_3OD.

In view of the role of vinylpyrimidines and vinylpurines in the synthesis of cyclic and acyclic analogues of nucleosides, the fluorovinyl derivatives of nucleobases represent useful starting materials for biologically interesting molecules. In recent years much attention has been paid to heterocyclic nucleosides having an isoxazolidine moiety instead of a ribofuranose ring. The synthesis of modified isoxazolidine nucleosides using nitrones and N-vinyl nucleobases as dipolarophiles in 1,3 dipolar cycloadditions was the most convenient and simplest method [143]. Some of these nucleosides have been found to show high cytostatic activity [144,145].

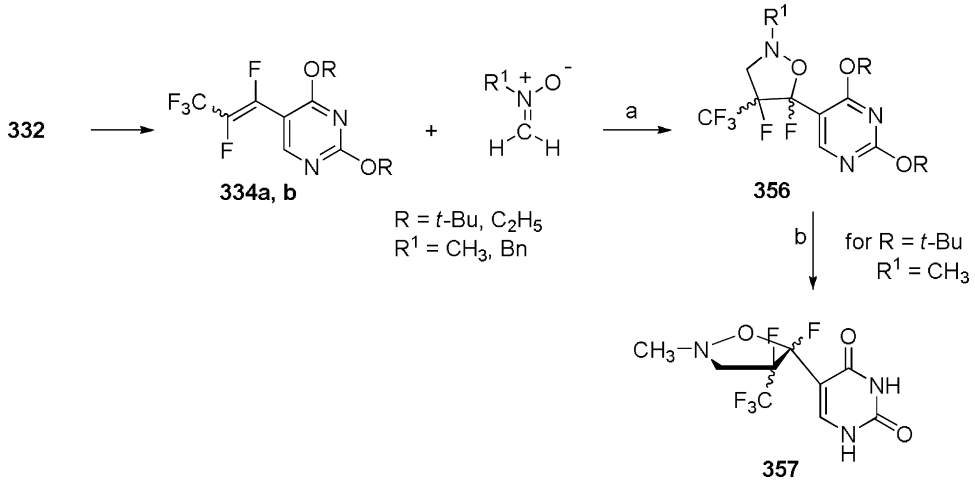
Wójtowicz and Koroniak described in 2012 a simple two-step synthesis of a new class of fluorinated isoxazolidinyl derivatives of pyrimidine [132]. The reactions proceed *via* the Suzuki-Miyaura coupling followed by highly regioselective 1,3-dipolar cycloaddition with nitrones. Removal of the pyrimidine protecting groups leads to a fluorinated isoxazolidine analogue of pseudouridine **357**. The direct 1,3-dipolar cycloaddition of 5-fluorovinyl pyrimidines **334a** and **334b** as dipolarophiles and N-methyl- and N-benzyl-methylenenitrones was performed according to Scheme 73.

The nitrones were generated *in situ* in the reaction of paraformaldehyde with the hydrochloride of the appropriate substituted hydroxylamine. Each time two diastereoisomers of the product were obtained, with one of them in significant dominance. The cycloaddition reactions were fully regiospecific. Moreover, only isomer *E* was actively involved in the 1,3-dipolar cycloaddition, while *Z* isomer remained almost unchanged. Standard attempts at removal of the protective ethyl and benzyl groups from pyrimidines **356** failed and did not produce the expected pseudouridine analogues. The isoxazolidine analogue of pseudouridine **357** was obtained as a result of non-standard hydrolysis of *t*-butyl derivative of **356,** without breaking the N–O bond of the isoxazolidine ring, in anhydrous THF using on almost equimolar amount of HCl.

The above presented isoxazolidine analogues are the first compounds in which the isoxazolidine ring mimicking the ribofuranose ring in C-nucleosides contains fluorine or a fluorinated substituent. It also appears that fluorinated *N*-vinyl nucleobases are good precursors for the synthesis of fluorinated isoxazolidine analogues of nucleosides.



Scheme 72. Reactions of (*E*)- and (*Z*)-(tetrafluoroprop-1-enyl)uracil **347b** with *t*-BuLi. Reagents: (a) *t*-BuLi, THF and (b) CD_3OD.



Scheme 73. The synthesis of fluoroisoxazolidines **356** and **357**. Reagents and conditions: (a) toluene, 80 °C and (b) 2–3 equiv. HCl, anhydrous THF.

6. Conclusion

There has been growing interest in the synthesis of modified nucleosides, especially highly modified derivatives and acyclic analogues. Fluorinated nucleosides and related analogues make up an important part of the extensively studied field of nucleoside analogues, which are a significant class of candidates for the antiviral drugs. They have been used as inhibitors of various enzymes, employed in DNA diagnostics and at least, applied as very effective antiviral agents. This trend has been enhanced the rising understanding of the influence of fluorine introduction on the modulation of pharmacological properties of modified molecules and increasing knowledge of the structure–activity relationships.

References

[1] D. O'Hagan, Chemical Society Reviews 37 (2008) 308–319.
[2] V.E. Marquez, C.K.-H. Tseng, H. Mitsuya, S. Aoki, J.A. Kelley, H. Ford Jr., J.S. Roth, S. Broder, D.G. Johns, J.S. Driscoll, Journal of Medicinal Chemistry 33 (1990) 978–985.
[3] K. Ruxrungtham, E. Boone, H. Ford Jr., J.S. Driscoll, R.T. Davey, H.C. Lane, Antimicrobial Agents and Chemotherapy 40 (1996) 2369–2374.
[4] A. Tokoyama, Y. Nakai, S. Yoneda, Y. Kurita, H. Niitani, Anti-Cancer Drugs 8 (1997) 574–581.
[5] K.W. Pankiewicz, Carbohydrate Research 327 (2000) 87–105.
[6] W.D. Meng, F.L. Qing, Current Topics in Medicinal Chemistry 6 (2006) 1499–1528.
[7] P. Liu, A. Sharon, C.K. Chu, Journal of Fluorine Chemistry 129 (2008) 743–766.
[8] X.L. Qiu, X.H. Xu, F.L. Qing, Tetrahedron 66 (2010) 789–843 (and references cited therein).
[9] H. Vorbrüggen, B. Bennua, Tetrahedron Letters 19 (1978) 1339–1342.
[10] S.W. Schneller, Current Topics in Medicinal Chemistry 2 (2002) 1087–1092.
[11] M. Ferrero, V. Gotor, Chemical Reviews 100 (2000) 4319–4347.
[12] S. Weller, K.M. Radomski, Y. Lou, D.S. Stein, Antimicrobial Agents and Chemotherapy 44 (2000) 2052–2060.
[13] Y.-H. Yeom, R.P. Rómmel, S.-H. Huang, M. Hua, R. Vince, C.L. Zimmerman, Antimicrobial Agents and Chemotherapy 33 (1989) 171–175.
[14] S.F. Innaimo, M. Seifer, G.S. Bisacchi, D.N. Standring, R. Zahler, R.J. Colonno, Antimicrobial Agents and Chemotherapy 41 (1997) 1444–1448.
[15] K.A. Sims, A.M. Woodland, Pharmacotherapy 26 (2006) 1745–1757.
[16] G.M. Blackburn, D.A. England, F. Kolkmann, Journal of the Chemical Society, Chemical Communications (1981) 930–932.
[17] G.M. Blackburn, D. Brown, S.J. Martin, M.J. Parratt, Journal of the Chemical Society, Perkin Transactions 1 (1987) 181–186.
[18] Y.-Y. Yang, W.-D. Meng, F.-L. Qing, Organic Letters 23 (2004) 4257–4259.
[19] K. Biggadike, A.D. Borthwick, D. Evans, A.M. Exall, B.E. Kirk, S.M. Roberts, L. Stephenson, P. Youds, A.M.Z. Slawin, D.J. Williams, Journal of the Chemical Society, Chemical Communications (1987) 251–253.
[20] A.D. Borthwick, D.N. Evans, B.E. Kirk, K. Biggadike, A.M. Exall, P. Youds, S.M. Roberts, D.J. Knight, J.A.V. Coates, Journal of Medicinal Chemistry 33 (1990) 179–186.
[21] Y.-Y. Yang, J. Xu, Z.-W. You, X.-H. Xu, X.-L. Qiu, F.-L Qing, Organic Letters 9 (2007) 5437–5440.
[22] A. Roy, S.W. Schneller, K.A. Keith, C.B. Hartline, E.R. Kern, Bioorganic and Medicinal Chemistry 13 (2005) 4443–4449.
[23] A. Roy, T. Serbessa, S.W. Schneller, Bioorganic and Medicinal Chemistry 14 (2006) 4980–4986.
[24] G.V.P. Madhavan, D.P.C. McGee, R.M. Rydzewski, R. Boehme, J.C. Martin, E.J. Prisbe, Journal of Medicinal Chemistry 31 (1988) 1798–1804.
[25] X.-Q. Yin, S.W. Schneller, Tetrahedron Letters 46 (2005) 7535–7538.
[26] L.S. Jeong, S.J. Yoo, K.M. Lee, M.J. Koo, W.J. Choi, H.O. Kim, H.R. Moon, M.Y. Lee, J.G. Park, S.K. Lee, M.W. Chun, Journal of Medicinal Chemistry 46 (2003) 201–203.
[27] R.T. Borchardt, B.T. Keller, U. Patel-Thombre, Journal of Biological Chemistry 259 (1984) 4353–4358.
[28] J. Wachtmeister, B. Classon, B. Samuelsson, Tetrahedron 53 (1997) 1861–1872.
[29] Y. Yang, F. Zheng, F.-L. Qing, Tetrahedron 67 (2011) 3388–3394.
[30] J. Wachtmeister, B. Classon, I. Kvarnstrom, B. Samuelsson, Nucleosides and Nucleotides 16 (1997) 809–814.
[31] A. Toyota, M. Aizawa, C. Habutani, N. Katagiri, C. Kaneko, Tetrahedron 51 (1995) 8783–8798.
[32] J. Wanga, U.S. Singh, R.K. Rawal, M. Sugiyama, J. Yoo, A.K. Jha, M. Scroggin, Z. Huang, M.G. Murray, R. Govindarajan, Y. Tanaka, B. Korba, C.K. Chu, Bioorganic and Medicinal Chemistry Letters 21 (2011) 6328–6331.
[33] Y. Morizawa, T. Nakayama, Y. Matsumura, K. Uchida, A. Yasuda, Bulletin of the Chemical Society of Japan 66 (1993) 2714–2719.
[34] H. Baumgartner, M. Bodenteich, H. Griengl, Tetrahedron Letters 29 (1988) 5745–5746.
[35] R. Hewitt, A. Gumble, L. Taylor, W. Wallace, Antibiotics Annual (1956) 722–729.
[36] G. Gumina, Y. Chong, Y. Choi, C.K. Chu, Organic Letters 2 (2000) 1229–1231.
[37] Y. Chong, G. Gumina, C.K. Chu, Tetrahedron: Asymmetry 11 (2000) 4853–4875.
[38] A.D. Borthwick, K. Biggadike, I.L. Paternoster, Bioorganic and Medicinal Chemistry Letters 3 (1993) 2577–2580.
[39] J. Wachtmeister, A. Muhlman, B. Classon, B. Samuelsson, Tetrahedron 55 (1999) 10761–10770.
[40] N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii, T. Takita, Journal of Antibiotics 39 (1986) 1623–1625.
[41] D.W. Norbeck, E. Kern, S. Hayashi, W. Rosenbrook, H. Sham, T. Herrin, J.J. Plattner, J. Erickson, J. Clement, R. Swanson, N. Shipkowitz, D. Hardy, K. Marsh, G. Arnett, W. Shannon, S. Broder, H. Mitsuya, Journal of Medicinal Chemistry 33 (1990) 1281–1285.
[42] Y. Wang, G.W.J. Fleet, F.X. Wilson, R. Storer, P.L. Myers, C.J. Wallis, O. Doherty, D.J. Watkin, K. Vogt, D.R. Witty, J.M. Peach, Tetrahedron Letters 32 (1991) 1675–1679.
[43] G.D. Vite, J.A. Tino, R. Zahler, V. Goodfellow, A.V. Tuomari, B. McGeever-Rubin, A.K. Field, Bioorganic and Medicinal Chemistry Letters 3 (1993) 1211–1214.
[44] T. Gharbaoui, M. Legraverend, O. Ludwig, E. Bisagni, A.-M. Aubertin, L. Chertanova, Tetrahedron 51 (1995) 1641–1652.
[45] Y. Sato, K. Ueyama, T. Maruyama, D.D. Richman, Nucleosides and Nucleotides 15 (1996) 109–119.
[46] Y. Li, S. Mao, M.W. Hager, K.D. Becnel, R.F. Schinazi, D.C. Liotta, Bioorganic and Medicinal Chemistry Letters 17 (2007) 3398–3401.
[47] T. Sekiyama, S. Hatsuya, Y. Tanaka, M. Uchiyama, N. Ono, S. Iwayama, M. Oikawa, K. Suzuki, M. Okunishi, T. Tsuji, Journal of Medicinal Chemistry 41 (1998) 1284–1298.
[48] R. Csuk, G. Thiede, Tetrahedron 55 (1999) 739–750.
[49] Y.R. Lee, J.-H. Park, R. Jeon, L.S. Jeong, M.W. Chun, H.-D. Kim, Nucleosides, Nucleotides and Nucleic Acids 20 (2001) 677–679.
[50] J.-H. Park, M.-H. Choi, L.S. Jeong, M.W. Chun, H.-D. Kim, Nucleosides, Nucleotides and Nucleic Acids 22 (2003) 955–957.

[51] C.H. Oh, J.H. Hong, Nucleosides, Nucleotides and Nucleic Acids 26 (2007) 403–411.
[52] T.C. Rosen, E. De Clercq, J. Balzarini, G. Haufe, Organic & Biomolecular Chemistry 2 (2004) 229–237.
[53] A. Kim, J.H. Hong, European Journal of Medical Chemistry 42 (2007) 487–493.
[54] S. Zhou, J.M. Breitenbach, K.Z. Borysko, J.C. Drach, E.R. Kern, E. Gullen, Y.-C. Cheng, Journal of Medicinal Chemistry 47 (2004) 566–575.
[55] R. Wang, M.B. Ksebati, J.C. Drach, J. Zemlicka, Nucleosides, Nucleotides and Nucleic Acids 20 (2001) 329–332.
[56] S. Zhou, E.R. Kern, E. Gullen, Y.-C. Cheng, J.C. Drach, S. Matsumi, H. Mitsuya, J. Zemlicka, Journal of Medicinal Chemistry 47 (2004) 6964–6972.
[57] C. Li, M.N. Prichard, B.E. Korba, J.C. Drach, J. Zemlicka, Bioorganic and Medicinal Chemistry 16 (2008) 2148–2155.
[58] W. Saenger, Principles of Nucleic Acid Structure, Springer Verlag, New York, 1984.
[59] B.A. Schweitzer, E.T. Kool, Journal of Organic Chemistry 59 (1994) 7238–7242.
[60] S. Moran, R.X.-F. Ren, S. Rumney, E.T. Kool, Journal of the American Chemical Society 119 (1997) 2056–2057.
[61] B.M. O'Neill, J.E. Ratto, K.L. Good, D.C. Tahmassebi, S.A. Helquist, J.C. Morales, E.T. Kool, Journal of Organic Chemistry 67 (2002) 5869–5875.
[62] G. Mathis, J. Hunziker, Angewandte Chemie International Edition 41 (2002) 3203–3205.
[63] J.S. Lai, E.T. Kool, Chemistry-A European Journal 11 (2005) 2966–2971.
[64] N. Griesang, C. Richert, Tetrahedron Letters 43 (2002) 8755–8758.
[65] J. Parsch, J.W. Engels, Helvetica Chimica Acta 83 (2000) 1791–1808.
[66] A.E. Klopffer, J.W. Engels, Nucleosides, Nucleotides and Nucleic Acids 22 (2003) 1347–1350.
[67] J. Haas, T. Mueller-Kuller, S. Klein, J.W. Engels, Nucleosides, Nucleotides and Nucleic Acids 26 (2007) 865–868.
[68] F. Seela, X. Peng, S. Budow, Current Organic Chemistry 11 (2007) 427–462.
[69] A.B. Eldrup, M. Prhavc, J. Brooks, B. Bhat, T.P. Prakash, Q. Song, S. Bera, N. Bhat, P. Dande, P.D. Cook, C.F. Bennett, S.S. Carroll, R.G. Ball, M. Bosserman, C. Burlein, L.F. Colwell, J.F. Fay, O.A. Flores, K. Getty, R.L. LaFemina, J. Leone, M. MacCoss, D.R. McMasters, J.E. Tomassini, D. von Langen, B. Wolanski, D.B. Olsen, Journal of Medicinal Chemistry 47 (2004) 5284–5297.
[70] F. Seela, K. Xu, P. Chittepu, Synthesis (2006) 2005–2012.
[71] F. Seela, P. Chittepu, H. Eickmeier, Acta Crystallographica Section C 62 (2005) 231–233.
[72] F. Seela, K. Xu, P. Chittepu, X. Ming, Nucleosides, Nucleotides and Nucleic Acids 2 (2007) 6607–6610.
[73] F. Seela, K. Xu, Helvetica Chimica Acta 91 (2008) 1083–1105.
[74] X. Peng, H. Li, F. Seela, Nucleic Acids Research (2006) 5987–6000.
[75] B.K. Bhattacharya, T.S. Rao, G.R. Revankar, Journal of the Chemical Society, Perkin Transactions 1 (1995) 1543–1550.
[76] B.K. Bhattacharya, J.O. Ojwang, R.F. Rando, J.H. Huffman, G.R. Revankar, Journal of Medicinal Chemistry 38 (1995) 3957–3966.
[77] H.G. Howell, P.R. Brodfuehrer, S.P. Brundidge, D.A. Benigni, C. Sapino Jr., Journal of Organic Chemistry 53 (1988) 85–88.
[78] X. Guo, Y. Li, L. Tao, Q. Wang, S. Wang, W. Hu, Z. Pan, Q. Yang, Y. Cui, Z. Ge, L. Dong, X. Yu, H. An, C. Song, J. Chang, Bioorganic and Medicinal Chemistry Letters 21 (2011) 6770–6772.
[79] P. Naus, R. Pohl, I. Votruba, P. Dzubak, M. Hajduch, R. Ameral, G. Birkus, T. Wang, A.S. Ray, R. Mackman, T. Cihlar, M. Hocek, Journal of Medicinal Chemistry 53 (2010) 460–470.
[80] P. Naus, P. Perlokova, R. Pohl, M. Hocek, Collection of Czechoslovak Chemical Communications 76 (2011) 957–988.
[81] E.C. Joseph, J.A. Rees, A. Dayan, Toxicologic Pathology 24 (1996) 436–450.
[82] V. Bavetsias, C. Sun, N. Bouloc, J. Reynisson, P. Workman, S. Linardopoulos, E. McDonald, Bioorganic and Medicinal Chemistry Letters 17 (2007) 6567–6571.
[83] V.O. Iaroshenko, D.V. Sevenard, D.M. Volochnyuk, Y. Wang, A. Martiloga, A.O. Tolmachev, Synthesis 11 (2009) 1865–1875.
[84] V.O. Iaroshenko, D. Ostrovskyi, A. Petrosyan, S. Mkrtchyan, A. Villinger, P. Langer, Journal of Organic Chemistry 76 (2011) 2899–2903.
[85] G.B. Elion, P.A. Furman, J.A. Fyfe, P. De Miranda, L. Beauchamp, H.J. Schaeffer, Proceedings of the National Academy of Sciences of the United States of America 74 (1977) 5716–5720.
[86] J.C. Martin, D.P. McGee, G.A. Jeffrey, D.W. Hobbs, D.F. Smee, T.R. Matthews, J.P. Verheyden, Journal of Medicinal Chemistry 29 (1986) 1384–1389.
[87] H.J. Schaeffer, L. Beauchamp, P. de Mir, G.B. Elion, D.J. Bauer, P. Collins, Nature 272 (1978) 583–585.
[88] M.R. Harnden, R.L. Jarvest, T.H. Bacon, M.R. Boyd, Journal of Medicinal Chemistry 30 (1987) 1636–1642.
[89] D.F. Smee, R. Boehme, M. Chernow, B.P. Binko, T.R. Matthews, Biochemical Pharmacology 34 (1985) 1049–1056.
[90] D.F. Smee, J.C. Martin, J.P.H. Verheyden, T.R. Matthews, Antimicrobial Agents and Chemotherapy 23 (1983) 676–682.
[91] G.A. Hospers, A. Calogero, A. van Waarde, P. Doze, W. Vaalburg, N.H. Mulder, E.F. De Vries, Cancer Research 60 (2000) 1488–1491.
[92] E.F. De Vries, A. Van Waarde, M.C. Harmsen, N.H. Mulder, W. Vaalburg, G.A. Hospers, Nuclear Medicine and Biology 27 (2000) 113–119.
[93] M.M. Alauddin, P.S. Conti, Nuclear Medicine and Biology 25 (1998) 175–180.
[94] H.J. Bohm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Muler, U. Obst-Sander, M. Stahl, ChemBioChem 5 (2004) 637–643.
[95] C. Isanbor, D. O'Hagan, Journal of Fluorine Chemistry 127 (2006) 303–319.
[96] M.M. Alauddin, P.S. Conti, S.M. Mazza, F.M. Hamzeh, J.R. Lever, Nuclear Medicine and Biology 23 (1996) 787–792.
[97] H. Cai, D. Yin, L. Zhang, Y. Wang, Journal of Fluorine Chemistry 127 (2006) 837–841.
[98] H. Cai, D. Yin, L. Zhang, X. Yang, X. Xu, W. Liu, X. Zheng, H. Zhang, J. Wang, Y. Xu, D. Cheng, M. Zheng, Y. Han, M. Wu, Y. Wang, Nuclear Medicine and Biology 34 (2007) 717–725.
[99] M. Grote, S. Noll, B. Noll, B. Johannsen, W. Kraus, Canadian Journal of Chemistry 82 (2004) 513–523.
[100] S. Prekupec, D. Svedruzic, T. Gazivoda, D. Mrvos-Sermek, A. Nagl, M. Grdisa, K. Pavelic, J. Balzarini, E. De Clercq, G. Folkers, L. Scapozza, M. Mintas, S. Raic-Malic, Journal of Medicinal Chemistry 46 (2003) 5763–5772.
[101] S. Raic-Malic, A. Johayem, S.M. Ametamey, S. Batinac, E. De Clercq, G. Folkers, L. Scapozza, Nucleosides, Nucleotides and Nucleic Acids 23 (2004) 1707–1721.
[102] S. Prekupec, D. Makuc, J. Plavec, L. Suman, M. Kralj, K. Pavelic, J. Balzarini, E. De Clercq, M. Mintas, S. Raic-Malic, Journal of Medicinal Chemistry 50 (2007) 3037–3045.
[103] S. Kristafor, T. Gazivoda, M. Cetina, D. Makuc, J. Plavec, S. Raic-Malic, Journal of Molecular Structure 923 (2009) 19–23.
[104] M. Hua, P.M. Korkowski, R. Vince, Journal of Medicinal Chemistry 30 (1987) 198–200.
[105] J. Zemlicka, Nucleosides, Nucleotides and Nucleic Acids 16 (1997) 1003–1012.
[106] S. Kristafor, A. Mescic, M. Cetina, S. Korunda, D. Makuc, J. Plavec, S. Raic-Malic, Journal of Fluorine Chemistry 132 (2011) 573–578.
[107] S. Gouault-Bironneau, A. Sene, J.-M. Catel, T. Lequeux, Journal of Fluorine Chemistry 129 (2008) 848–851.
[108] M.-H. Choi, C.-K. Lee, H.-D. Kim, Archives of Pharmacal Research 33 (2010) 197–202.
[109] E. De Clercq, Clinical Microbiology Reviews 16 (2003) 569–596.
[110] E. De Clercq, A. Holy, Nature Reviews Drug Discovery 4 (2005) 928–940.
[111] A. Holy, Current Pharmaceutical Design 9 (2003) 2567–2592.
[112] E. De Clercq, Antiviral Research 75 (2007) 1–13.
[113] J. Balzarini, A. Holy, J. Jindrich, H. Dvorakova, Y. Hao, R. Snoeck, P. Herdewijn, D.G. Johns, E. De Clercq, Proceedings of the National Academy of Sciences of the United States of America 88 (1991) 4961–4965.
[114] J. Balzarini, C.-F. Perno, D. Schols, E. De Clercq, Biochemical and Biophysical Research Communications 178 (1991) 329–335.
[115] J. Jindrich, A. Holy, H. Dvorakova, Collection of Czechoslovak Chemical Communications 58 (1993) 1645–1667.
[116] O. Baszczynski, P. Jansa, M. Dracinsky, B. Klepetarova, A. Holy, I. Votruba, E. de Clercq, J. Balzarini, Z. Janeba, Bioorganic & Medicinal Chemistry 19 (2011) 2114–2124.
[117] W. Chen, M.T. Flavin, R. Filler, Z.-Q. Xu, Journal of the Chemical Society, Perkin Transactions 1 (1998) 3979–3988.
[118] K. Pomeisl, I. Votruba, A. Holy, R. Pohl, Collection of Czechoslovak Chemical Communications 71 (2006) 595–624.
[119] P. Jansa, V. Kolman, A. Kostinova, M. Dracinsky, H. Mertlikova-Kaiserova, Z. Janeba, Collection of Czechoslovak Chemical Communications 76 (2011) 1187–1198.
[120] T. Ostrowski, B. Wroblowski, R. Busson, J. Rozenski, E. De Clercq, M.S. Bennett, J.N. Champness, W.C. Summers, M.R. Sanderson, P.J. Herdewijn, Journal of Medicinal Chemistry 41 (1998) 4343–4353.
[121] R. Kumar, M. Nath, D.L.J. Tyrrell, Journal of Medicinal Chemistry 45 (2002) 2032–2040.
[122] A.A. Van Aerschot, P. Mamos, N.J. Weyns, S. Ikeda, E. De Clercq, P.A. Herdewijn, Journal of Medicinal Chemistry 36 (1993) 2938–2942.
[123] S. Pal, B. Bera, V. Nair, Bioorganic and Medicinal Chemistry 10 (2002) 3615–3618.
[124] E.W. Van Tilburg, M. Gremmen, M. De Groote, A.P. Ijzerman, Bioorganic and Medicinal Chemistry 11 (2003) 2183–2192.
[125] L.A. Agrofoglio, I. Gillaizeau, Y. Saito, Chemical Reviews 103 (2003) 1875–1916 (and references cited therein).
[126] A.S. Jones, S.G. Rahim, R.T. Walker, E. De Clercq, Journal of Medicinal Chemistry 24 (1981) 759–760.
[127] E. De Clercq, C. Desgranges, P. Herdewijn, I.S. Sim, A.S. Jones, M.J. McLean, R.T. Walker, Journal of Medicinal Chemistry 29 (1986) 213–217.
[128] P.L. Coe, M.R. Harnden, A.S. Jones, S.A. Noble, R.T. Walker, Journal of Medicinal Chemistry 25 (1982) 1329–1334.
[129] H. Wójtowicz-Rajchel, M. Migas, H. Koroniak, Journal of Organic Chemistry 71 (2006) 8842–8846.
[130] H. Koroniak, P. Karwatka, D. Pluskota, P. Fiedorow, A. Jankowski, Journal of Fluorine Chemistry 71 (1995) 135–137.
[131] H. Wójtowicz-Rajchel, I. Bednarczyk, A. Katrusiak, H. Koroniak, Mendeleev Communications 14 (2004) 63–65.
[132] H. Wójtowicz-Rajchel, H. Koroniak, Journal of Fluorine Chemistry 135 (2012) 225–230.
[133] V. Nair, B. Bera, E.R. Kern, Nucleosides, Nucleotides and Nucleic Acids 22 (2003) 115–127.
[134] Q. Shen, J.H. Hong, Nucleosides, Nucleotides and Nucleic Acids 27 (2008) 213–223.
[135] L.L. Bennett, P.W. Allan, L.M. Rose, R.N. Comber, J.A. Secrist, Molecular Pharmacology 29 (1986) 383–390.
[136] P. Chirakul, S.Th. Sigurdsson, Tetrahedron Letters 44 (2003) 6899–6901.
[137] U.M. Nagele, M. Hanack, Liebigs Annalen der Chemie (1989) 847–852.
[138] B. Jiang, F. Zhank, W. Xiong, Tetrahedron 58 (2002) 265–270.

[139] H. Wójtowicz-Rajchel, H. Koroniak, A. Katrusiak, European Journal of Organic Chemistry (2008) 368–376.
[140] W.R. Dolbier Jr., X.X. Rong, Journal of Organic Chemistry 62 (1997) 1576–1577.
[141] R. Dalpozzo, A. De Nino, L. Maiuolo, A. Procopio, R. Romeo, G. Sindona, Synthesis (2002) 172–173.
[142] H. Wójtowicz-Rajchel, M. Pasikowska, A. Olejniczak, A. Katrusiak, H. Koroniak, New Journal of Chemistry 34 (2010) 894–902.
[143] U. Chiacchio, A. Padwa, G. Romeo, Current Organic Chemistry 13 (2009) 422–447, and references cited therein..
[144] U. Chiacchio, A. Corsaro, D. Iannazzo, A. Piperno, V. Pistara, A. Rescifina, R. Romeo, V. Valveri, A. Mastino, G. Romeo, Journal of Medicinal Chemistry 46 (2003) 3696–3702.
[145] O. Bortolini, A. De Nino, T. Eliseo, R. Gavioli, L. Maiuolo, B. Russo, F. Sforza, Bioorganic and Medicinal Chemistry 18 (2010) 6970–6976.