

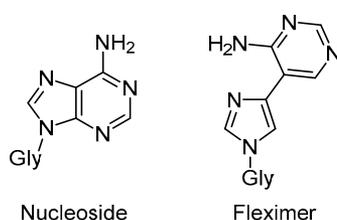
Nucleoside analogs with fleximer nucleobase

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This review article is devoted to the so-called fleximer nucleoside analogs, containing two or more planar moieties in the heterocyclic base, connected by a bond that permits rotation. Such analogs have been proposed as molecular probes for detecting enzyme–substrate interactions and studying the transcription and translation of nucleic acids, but subsequently have attracted the interest of researchers by their antiviral and antitumor activity. The methods used in the synthesis of such compounds, along with their structural features and also biological activity are considered in this review.

Keywords: pyrimidine, riboside, triazole, antitumor activity, antiviral activity, fleximer, nucleoside analogs.

The term "fleximers" was introduced in 2001 by the Seley research group,¹ referring to synthetic analogs of nucleosides in which the purine base has been "splitted" into two linked heterocycles – imidazole and pyrimidine. Initially intended as model compounds for studying the binding sites of enzymes and characterizing the interactions between proteins and nucleic acids, compounds of this type have subsequently shown remarkable antiviral and antitumor activity. In the light of recent events, there is a considerable interest in the possible applications of such compounds against coronavirus infections.² The category of fleximers can be extended also to several other synthetic nucleosides, the heterocyclic base of which contains two (or more) linked planar rings. All of them can be viewed as isosteric analogs of natural nucleosides that possess considerable pharmacological potential. The methods for synthesis, description of properties, and the biological activity of fleximer nucleosides are thoroughly considered in the current review article.

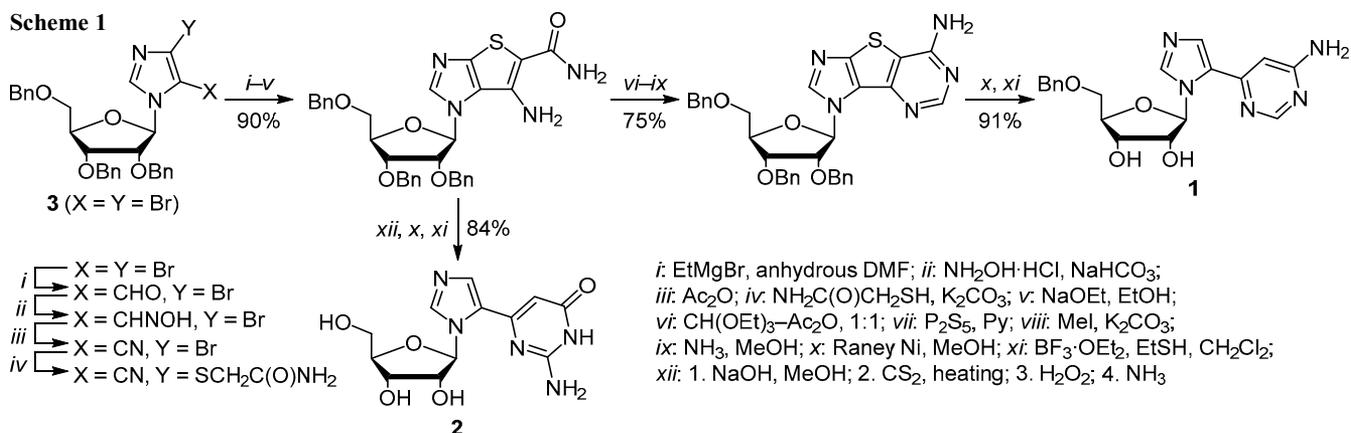
Routes of synthesis leading to fleximer nucleosides

The first fleximer nucleosides – isosteric analogs of adenosine **1** and guanosine **2** – were obtained from 4,5-dibromo-1-(2,3,5-tri-*O*-benzyl- β -D-ribofuranosyl)-1*H*-imidazole (**3**) through a rather involved multistep synthesis. The key step in the synthesis of the "splitted" structure of the

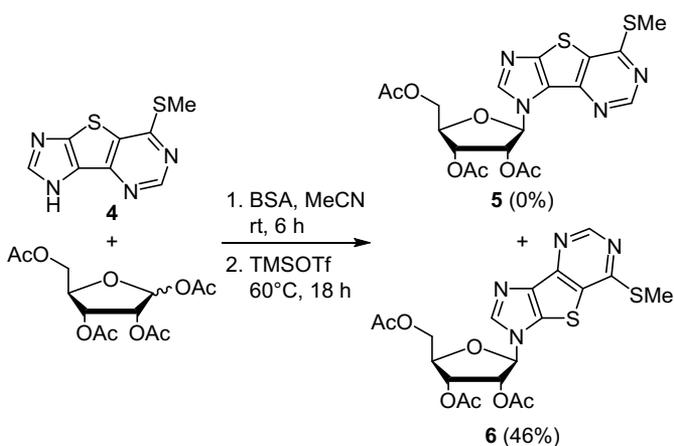
heterocyclic base was the assembly of a fused tricyclic system with a central thiophene ring. This tricyclic system was subjected to Raney nickel desulfurization, providing the desired fleximer¹ (Scheme 1). Similarly to any other synthesis of nucleoside analogs, there was the issue of which synthetic step would be most convenient for the formation of the glycosidic bond. The attempts to perform glycosylation of a previously assembled tricyclic base **4** did not quite succeed – instead of the expected mixture of glycosides **5** and **6**, only the nontarget isomer **6** was obtained in a moderate yield³ (Scheme 2). As a result of this, the strategy was changed to assembling the ring system on the basis of the nucleosidic precursor **3**.

The structures of the first synthesized fleximers **1** and **2** (Scheme 1) contained a bond between the C-5 carbon atom of imidazole ring and the C-6 carbon atom of pyrimidine ring (distal fleximers). The same research group later also obtained proximal fleximers with a conserved purine moiety, but with a different position of bond between the rings: between the C-4 carbon atom of imidazole and the C-5 carbon atom of the pyrimidine ring. The synthesis of these fleximers was achieved using a new route based on the palladium-catalyzed cross coupling, which was subsequently applied to the synthesis of nearly all described fleximer nucleoside analogs⁴ (Scheme 3).

Scheme 1

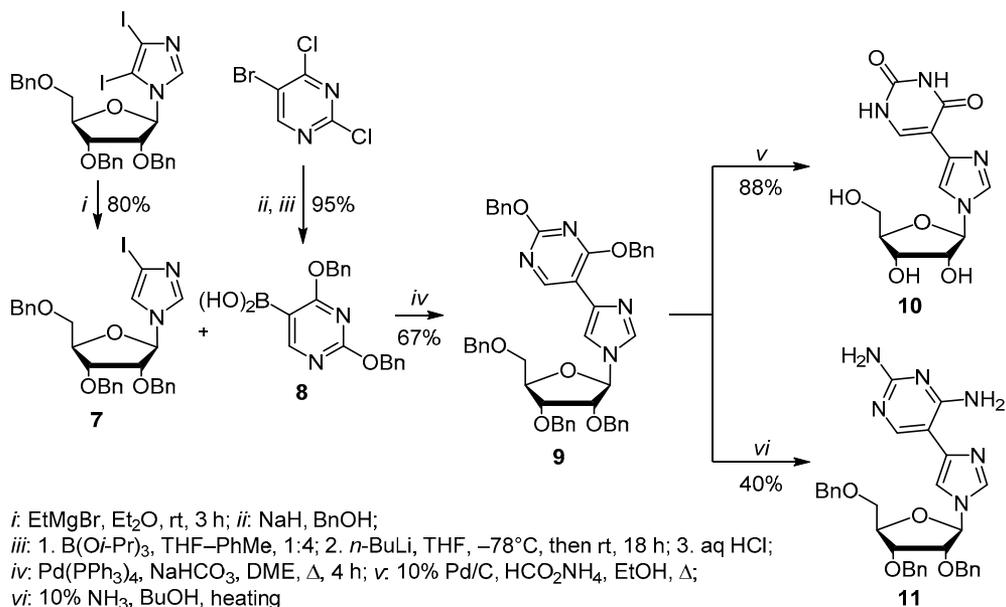


Scheme 2



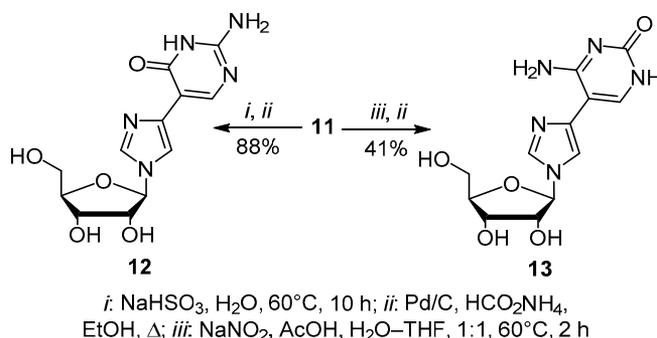
4-Iodo-1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-1*H*-imidazole (**7**) was used in a Suzuki reaction with boronic acid **8** in the presence of a palladium catalyst and the obtained fleximer precursor **9** was directly converted into xanthosine isostere **10** and into the substituted diamino derivative **11** (Scheme 3). Compound **11**, on the other

Scheme 3



hand, was used for the synthesis of fleximer guanosine analog **12** and isoguanosine analog **13**⁴ (Scheme 4). Similar methods provided access also to the proximal and distal fleximer 2'-deoxynucleosides,⁵ acyclic fleximer nucleoside analogs,^{2,6} as well as the fleximer analogs of neplanocin A, a carbocyclic nucleoside antibiotic.⁷

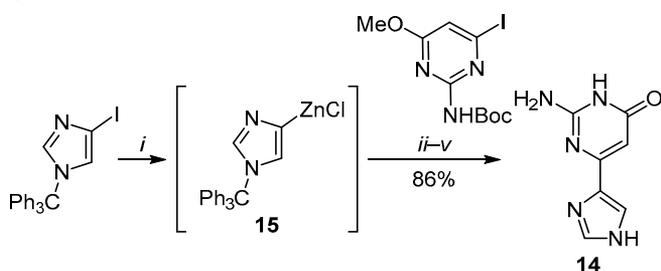
Scheme 4



The distal "flexible guanine" isomer **14** was obtained from imidazole organozinc derivative **15** (Scheme 5), while the same authors did not succeed in deprotecting the

proximal isomer.⁸ In more detail, synthetic methods for the nucleosides with "classical" fleximeric nucleobases have been described in a monograph that was published in 2018.⁹

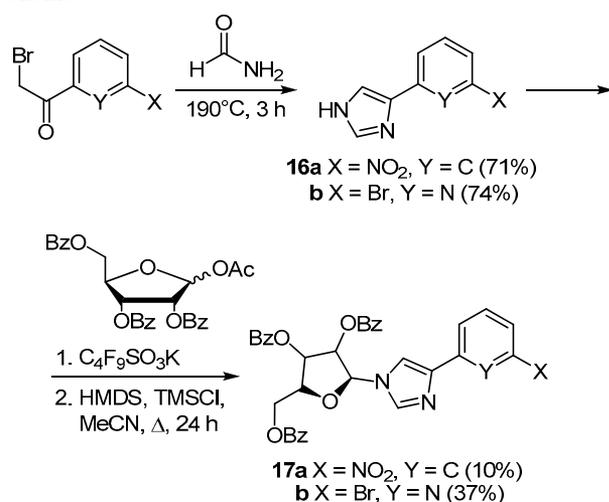
Scheme 5



i: 1. EtMgBr, THF, -78°C ; 2. ZnCl₂, rt, 2 h; *ii*: Pd(PPh₃)₄, CuI, THF, rt, 18 h; *iii*: AcOH, rt, 18 h; *iv*: TFA, rt, 18 h; *v*: BBr₃, EtOAc, rt, 72 h

Several fleximer nucleosides having significantly simpler structures were synthesized for modeling the process of genetic code recognition. In that case, the classic synthetic sequence was applied to the preparation of nucleoside analogs: the synthesis of compounds **16a,b** was followed by their glycosylation (Scheme 6). Fleximers **17a,b** were then converted through known procedures into the amino derivatives (X = NH₂) and functionalized at the amino group. The yields of compounds **17a,b** were in the range from 10 to 37%, probably due to the formation of isomeric products at the glycosylation stage.¹⁰

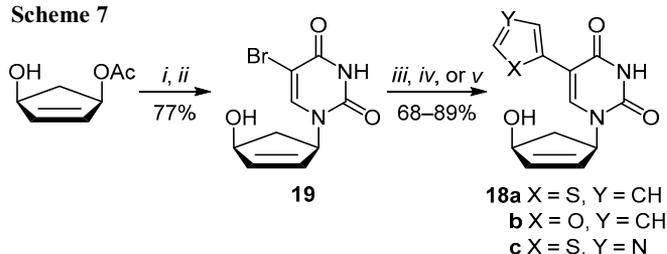
Scheme 6



Another class of fleximer nucleosides was created with the aim of searching for new antiviral and antitumor drugs, therefore pharmacologically active isosteres were chosen instead of natural purine nucleosides as a structural model. The synthesis of a series of "inverted" carbocyclic fleximers **18a–c**, in which a pyrimidine ring was linked to the pseudo-carbohydrate moiety, gave 68–89% yields in the key step. The bond between the pyrimidine ring and the second heterocycle was formed by a condensation reaction of 5-bromouracil derivative **19** with organostannanes

according to the Stille reaction¹¹ (Scheme 7). The same approach was also used for obtaining the derivatives with 2,3-dihydroxycyclopent-4-en-1-yl and 2,3-dihydroxycyclopentan-1-yl carbocycles.¹²

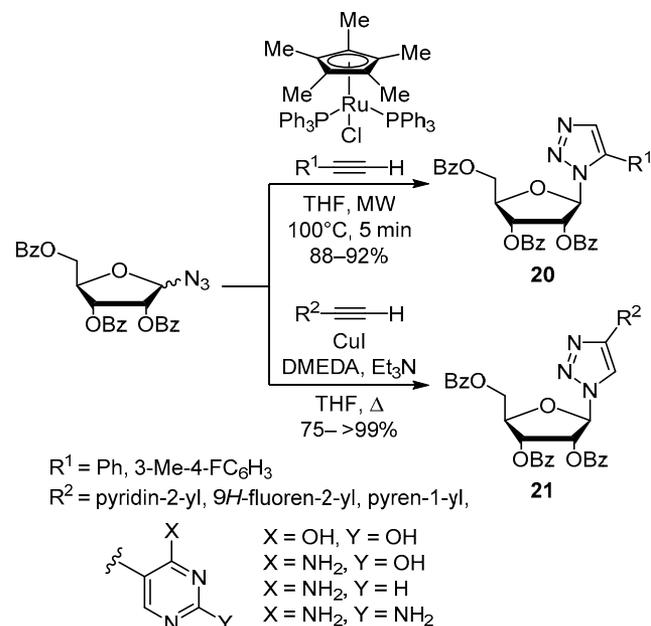
Scheme 7



i: 1-benzoyl-5-bromouracil, NaH, Pd₂(dba)₃, dppp, DMF, 55°C, 72 h;
ii: NH₃, MeOH, rt, 3 h; *iii*: 2-(tributylstannyl)thiophene, PdCl₂(PPh₃)₂, 1,4-dioxane, 120°C, 18 h (for **18a**); *iv*: 2-(tributylstannyl)furan, PdCl₂(PPh₃)₂, 1,4-dioxane, 120°C, 18 h (for **18b**);
v: 5-(tributylstannyl)thiazole, Pd(PPh₃)₄, THF, Δ, 72 h (for **18c**)

In many cases, click reactions were used for the fleximer synthesis, in particular Huisgen's cycloaddition of azides to alkynes. Distal fleximers **20** were obtained upon microwave irradiation in the presence of a ruthenium catalyst,¹³ while proximal nucleosides **21** were prepared by a copper-catalyzed Huisgen reaction¹⁴ (Scheme 8). The yields of the protected nucleosides ranged from 75 to >99%.

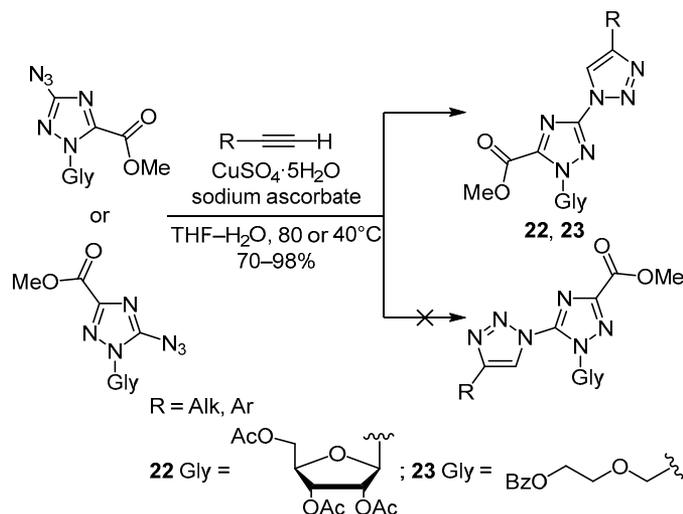
Scheme 8



Similar methods provided access to bistriazole fleximers, related to ribavirin (1-(β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide) – a known antiviral drug.¹⁵ Starting from protected structural analogs of ribavirin, containing an azido group at position 3 of the heterocyclic base, a total of 11 fleximer ribonucleosides **22** were synthesized, which had various alkyl and aryl substituents in the 1,2,3-triazole ring. Remarkably, the isomer with an

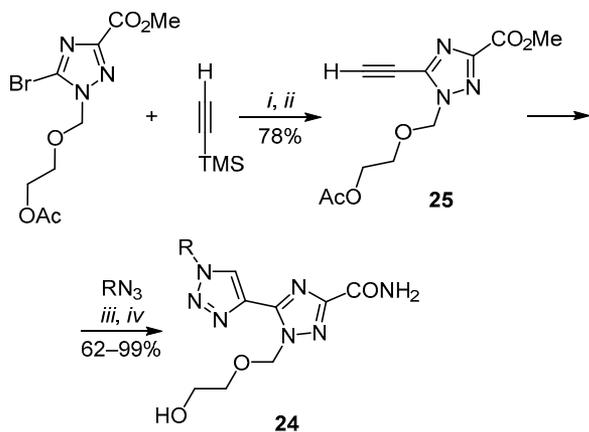
azide group at position 5 did not participate in cycloaddition reaction under the same conditions^{15a} (Scheme 9).

Scheme 9



Similarly, 10 acyclic bitriazole acyclic nucleosides **23**^{15b} were also synthesized (Scheme 9), while a series of 9 acyclic ribavirin fleximer analogs **24** containing a C–C bond between the triazole rings were obtained by a reaction of the protected acyclic nucleoside **25** with alkyl and aryl azides^{15c} (Scheme 10).

Scheme 10



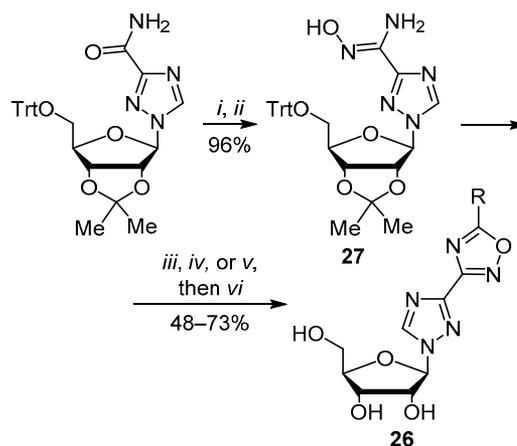
R = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-F₃CC₆H₄, 4-O₂NC₆H₄, (CH₂)₁₁Me, Bn, naphthalen-1-yl, (pyren-1-yl)methyl

i: Pd(PPh₃)₄, CuI, Et₃N, 1,4-dioxane, MW, 100°C, 25 min;
ii: KF, MeOH, rt, 2 h; *iii*: CuSO₄·5H₂O, sodium ascorbate, THF–H₂O, 45°C; *iv*: NH₃, MeOH, rt, 24 h

Analogues of ribavirin that contain aryl substituents at position 5 of 1,2,4-triazole ring can be viewed as a simplified variant of fleximer nucleosides. A series of 10 such ribosides were obtained in 72–91% yields from protected 5-bromoribavirin and arylboronic acids using a Suzuki reaction, that proceeded under microwave irradiation in PhMe,¹⁶ and 13 acyclic analogs too.¹⁷

The structure of triazolyloxadiazole ribonucleosides **26** seems to be closer to the initial concept of fleximers as purine nucleobase isosteres. They were obtained by cyclization of amidoxime **27** in the presence of tetrabutylammonium fluoride (TBAF)¹⁸ or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU)¹⁹ (Scheme 11).

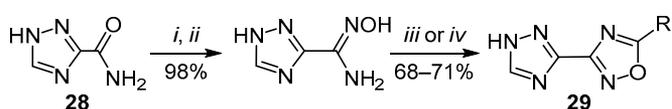
Scheme 11



i: TFAA, Py, CH₂Cl₂, 0–5°C, 12 h; *ii*: aq. NH₂OH, MeOH, rt, 12 h;
iii: CH(OEt)₃, TsOH, Δ, 3 h (R = H); *iv*: 1. RCOCl, Et₃N, CH₂Cl₂, rt, 1.5 h; 2. TBAF, PhMe, Δ, 4 h (R = Me, *i*-Pr, Ph); *v*: TBTU, DIPEA, rt, 10 h (R = NMe₂); *vi*: TFA–H₂O, rt, 40 min

Compounds **26** and 2'-deoxyribonucleosides containing the same bases were obtained also by a different route. Starting from 1*H*-1,2,4-triazole-3-carboxamide (**28**), the substituted triazolyloxadiazoles **29** were obtained in three steps in the overall yield of 68–71% (Scheme 12). The attempts at direct glycosylation of these bases according to the traditional procedure were not successful: the oxadiazole ring was destroyed. At the same time, these compounds appeared to be excellent substrates for recombinant purine nucleoside phosphorylases (PNP, EC 2.4.2.1), enzymes applied to the synthesis of various unnatural nucleosides by a transglycosylation reaction, essentially representing a nucleobase transfer.¹⁸ Although the substrate specificity of these enzymes was not very high,²⁰ the participation of bases **29** in the reaction indirectly confirmed the postulated isosterism of fleximer bases and purines.

Scheme 12

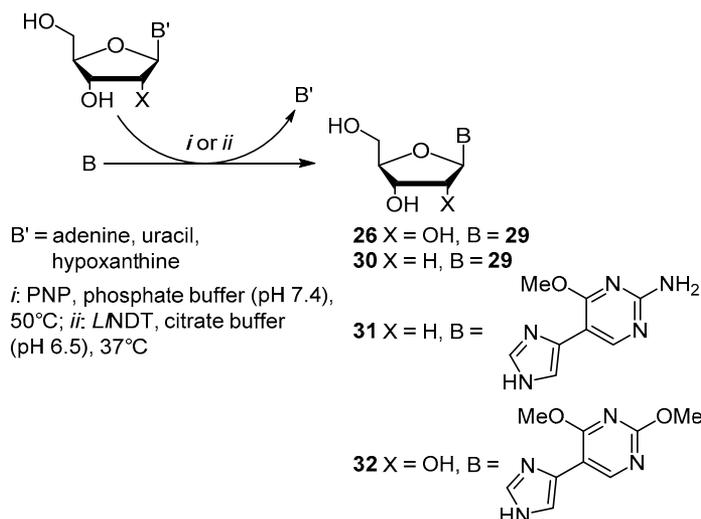


i: TFAA, Py, 1,4-dioxane, –5°C, 10 min; *ii*: aq. NH₂OH, EtOH, rt, 12 h;
iii: CH(OEt)₃, Δ, 3 h (R = H); *iv*: 1. RCOCl, Et₃N, CH₂Cl₂, 0°C, 1.5 h; 2. TBAF, PhMe, Δ, 4 h (R = Me, *i*-Pr, Ph)

It has been recently also shown that enzymatic transglycosylation enabled the preparation of "classic" fleximers. The catalyst in this process could be not only PNP from *E. coli*, but also nucleoside-2'-deoxyribosyl-transferase (LINDT, EC 2.4.2.6) from *L. leichmannii*,

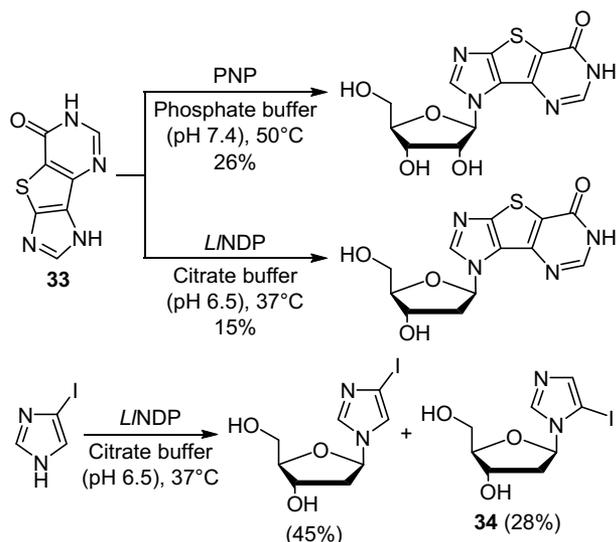
allowing to synthesize 2'-deoxyribonucleosides **30** and **31**. Due to the substrate specificity of these enzymes, the reaction proceeded mostly at N-1 position of the imidazole ring. Despite the fact that both the proximal and distal isomers of nucleobases participated in this reaction, only the proximal compounds **31** and **32** were synthetically accessible²¹ (Scheme 13).

Scheme 13



The distal isomers may be obtained from the enzymatic reaction products of tricyclic base **33**^{21a} by desulfurization on Raney nickel or Suzuki reaction of nucleoside **34** with arylboronic acids^{21b} (Scheme 14).

Scheme 14

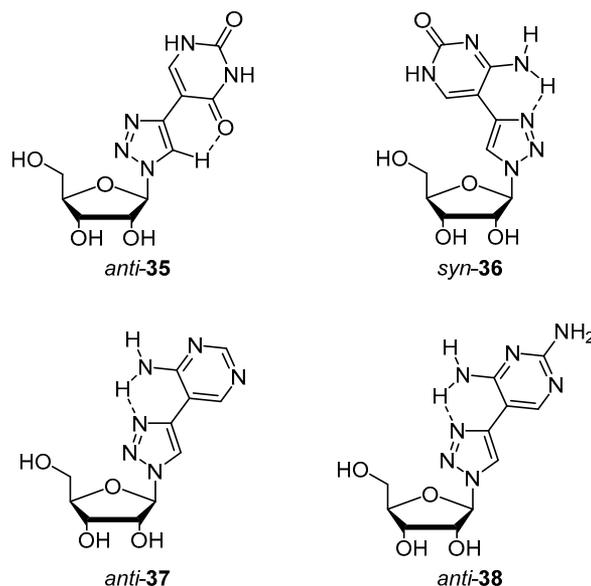


The structural features of fleximers

The fleximer nucleoside analogs were initially designed on the basis of the assumption that mutual rotation of the rings in the modified nucleobase should increase the accessibility of the structure to interactions within enzyme active sites.³ These compounds were presented as

"molecular chameleons" that could adapt to their environment and therefore, presumably, be more active in the roles of enzyme inhibitors or agonists.⁴ However, a question was immediately raised about the actual degree of flexibility in these fleximers. The theoretically free rotation of the rings relative to each other must in reality be limited by intramolecular and intermolecular interactions. The comparative conformational analysis of fleximers **1** and **2** and the natural purine nucleosides, relying on the data of one-dimensional differential NOE spectra and *ab initio* calculations showed that the pool of N conformations (north conformations) in the case of fleximers was considerably larger than for natural purines.²² This could, for example, explain the unexpected earlier observation: fleximer guanosine analog **2** inhibited *S*-adenosyl-L-homocysteine hydrolase (EC 3.3.1.1) – an enzyme that is specific for adenosine, while fleximer **1** (an adenosine analog) did not interact with this enzyme.²³ Both ribosides and acyclic fleximers²⁴ predominantly existed in their *anti* conformations in solutions (compounds **35–38**, Fig. 1). Computational structure modeling of the "classic" imidazole-pyrimidine fleximers showed that the energy barrier for rotation around the C–C bond linking the heterocycles was equal to about 40 kJ/mol. Besides that, the calculated bond energies for fleximer–pyrimidine pairs showed that the hydrogen bond properties in these modified nucleobases imitated the properties of the respective natural purines. The interaction with carbohydrate moiety often led to preferred nonplanar conformation of the two rings: the rings were oriented at 25–40° relative to each other, while the energy barrier was decreased.²⁵

X-ray structural studies of bitriazole fleximers **22** (Scheme 9) showed that the triazole rings in the bitriazole base were coplanar.^{15a} The nitrogen-containing heterocycles were also coplanar in the nucleobase moieties of compounds **35–38**, which were obtained from the substituted compounds **21** (Scheme 8), as their

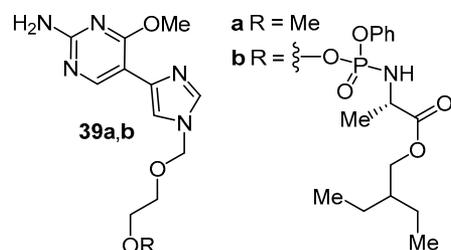
Figure 1. The conformations of fleximer ribosides **35–38**.

conformation was stabilized by the additional hydrogen bonds between the rings (Fig. 1).

The biological activity of fleximers

The fleximers intended for studying enzyme–substrate interactions showed a broad range of biological activity, as should be expected. Similarly to other nucleoside analogs, they exhibited antiviral and antitumor properties associated with their isosteric similarity to the natural nucleobases. The justification for such activity is considered in detail in several review articles.²⁶

The interest of researchers has been most attracted by the varied antiviral activity of fleximers. Acyclic analogs **39a,b** of the "classic" fleximers (Fig. 2) are active against the coronaviruses HCoV-NL63 and MERS,^{2,6} the filoviruses, in particular various strains of the Ebola virus,²⁷ while the ribavirin-type fleximers have shown activity against the hepatitis C virus (compound **26** (R = Ph, Scheme 11) had half maximum inhibitory concentration (IC₅₀) of 8.8 μg/ml, half maximum cytotoxic concentration (CC₅₀) of 380 μg/ml), as well as against the herpes and influenza A viruses,¹⁸ and the tobacco mosaic virus.^{15b}



39a EC₅₀ 8.8 ± 1.5 μM (HCoV-NL63)
CC₅₀ 120 ± 37 μM (Vero-118)
EC₅₀ 27 μM (MERS-CoV)
CC₅₀ 149 ± 6.8 μM (Vero-118)

39b EC₅₀ 44 ± 13 μM (EBOV)
EC₅₀ 20 ± 10 μM (SUDV)
CC₅₀ >100 μM (HeLa)

Figure 2. Acyclic analogs of "classic" fleximers – compounds **39a,b** showing antiviral activity.

A detailed study by Seley-Radtke and coworkers revealed the relationships between the structure of functionalized pyrimidine ring and the activity of imidazole-pyrimidine fleximers against the Ebola virus, as well as mentioned some unpublished data on antinflavivirus properties of the "classic" fleximers.²⁴ The correlation between the biological properties and structural features of "flexible" nucleobases was discussed in a monograph published in 2014.²⁸

Acyclic bitriazole nucleosides **24** (Scheme 10) exhibited antiproliferative activity against the drug-resistant pancreatic cancer cell line MIA PaCa-2, which is associated with caspase-dependent apoptosis. These compounds were also characterized with respect to their immunomodulatory properties. Interestingly, the most active among acyclic bitriazole nucleosides **24** was the

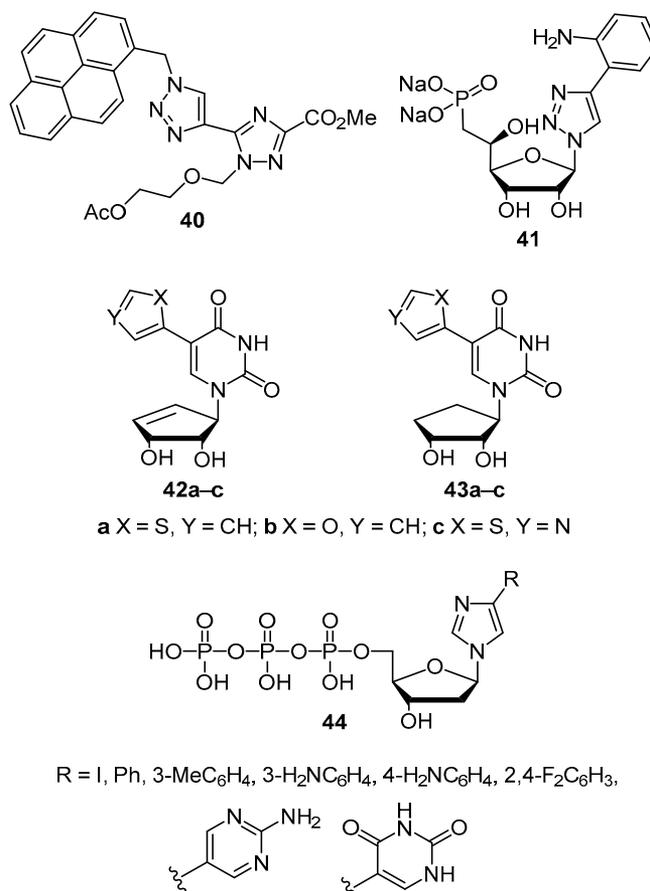


Figure 3. Acyclic fleximer nucleoside analog **40**, carbocyclic fleximer nucleosides **42a–c**, **43a–c**, and the fleximer nucleosides **41**, **44**.

protected intermediate **40** containing (pyren-1-yl)methyl substituent at the 1,2,3-triazole ring (Fig. 3), and not the nucleoside derived from it.^{15c} Antiproliferative activity against the cell line MIA PaCa-2 was also exhibited by close structural analogs of bitriazole fleximers, ribonucleosides containing an arylamino group at the 1,2,4-triazole ring.²⁹

There is a scarcity of available information in the literature on the biological targets and established mechanisms of action for fleximer nucleosides. As already pointed out, the distal fleximer guanosine analog **2** (Scheme 1) inhibited the *S*-adenosyl-L-homocysteine hydrolase,²³ while its triphosphate was an excellent substrate for human fucose-1-phosphate guanylyl-transferase (EC 2.7.7.30).³⁰ Compound **40** activated caspase-3 and caspase-7 (EC 3.4.22.56 and EC 3.4.22.60, respectively), causing apoptosis of cancer cells, while simultaneously acting as agonist of the TLR7 receptor (toll-like receptor 7) that initiates immune response mechanisms.^{15c} Compound **41** inhibited the cytosolic 5'-nucleotidase II (EC 3.1.3.5),^{14b} while carbocyclic nucleosides **42a–c** and **43a–c** (Fig. 3) inhibited adenosine deaminase (EC 3.5.4.4).¹²

Proximal nucleotides **44** (Fig. 3) were studied in the role of substrates for DNA polymerases. Commercially available DNA polymerases were used: endonuclease-free

Klenow fragment KF (exo-), Deep Vent (exo-), and terminal deoxynucleotidyl transferase. Triphosphates **44** were found to act as substrates for all of these enzymes, with adenine as the preferred base pair during DNA chain elongation. The derivative with 3-aminophenyl substituent was integrated in the chain opposite to adenine by the KF polymerase (exo-) only 37 times less effectively than the native thymidine triphosphate. The chain elongation terminated after the inclusion of a single arylimidazole nucleotide.³¹ This observation suggests that a possible mechanism for the antiviral action of compounds **39a,b** (Fig. 2) relies on the termination of viral nucleic acid replication.

A quite significant number of interesting compounds in which planar rings of the nucleobases are separated by more than one bond are described in a review article³² and a series of subsequent publications.³³ Compounds that are structurally related to fleximers have already entered pharmaceutical development. Thus, pevonedistat (MLN4924)³⁴ is currently in phase I of clinical trials against acute myeloid leukemia, while regadenoson (CVT-3146, Lexiscan) has been approved by the U.S. Food and Drug Agency (FDA) as agonist of adenosine receptor A_{2A} for the treatment of cardiovascular diseases. While a question may be raised whether such compounds should be categorized as fleximers, as the majority of them are not isosteres of purine or pyrimidine nucleosides, it should be recognized that the conformational flexibility of the heterocyclic moiety may affect their biological activity.

In the conclusion, it should be noted that even though the majority of key synthetic work devoted to fleximer nucleosides has been published many years ago, the most promising studies from the aspect of biological properties and medicinal chemistry applications are quite recent. This gives a reason to hope that the research involving fleximer nucleosides may have a great future.

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