SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Synthesis of new type of peptide-nucleic acids and furanose ring modified nucleosides

by Bege Miklós

Supervisor: Prof. Dr. Anikó Borbás

University of Debrecen

Doctoral School of Pharmaceutical Sciences

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By Bege Miklós, PharmD

Supervisor: Prof. Dr. Borbás Anikó, DSc

Doctoral School of Pharmaceutical Sciences, University of Debrecen

Head of the **Examination Committee**:	Prof. Dr. Árpád Tósaki, DSc
Members of the Examination Committee:	Prof. Dr. Tibor Kurtán, DSc
	Prof. Dr. Pál Perjési, PhD

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Head of the **Defense Committee**:	Prof. Dr. Árpád Tósaki, DSc
Reviewers:	Prof. Dr. Zsolt Szakonyi, DSc
	Dr. László Juhász, PhD
Members of the Defense Committee:	Prof. Dr. Tibor Kurtán, DSc
	Prof. Dr. Pál Perjési, PhD

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The publicity of the event is provided via an online videoconference. Whoever wishes to participate is kindly requested to write an e-mail to the miksaprof@gmail.com address by 2022. May 10. 16:00. After that, due to technical reasons, there is no opportunity to join the defense procedure.

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List of abbreviations

ATP: adenosine-triphosphate

cAMP= cyclic-adenosine-monophosphate

cGMP= cyclic-guanosine-monophosphate

DCC= dicyclohexyl-carbodiimide

DNA= deoxyribonucleic acid

DPAP= 2,2-dimethoxy-2-phenylacetophenone

Eq.= equivalent

Fmoc= 9-fluorenyl-methoxycarbonyl

hA: homoadenosine

hU: homouridine

LNA: locked nucleic acid

NAD= nicotinamide adenine dinucleotide

NADP= nicotinamide adenine dinucleotide-phosphate

PNA= peptide nucleic acid

PRNA: peptide ribonucleic acid

RNA= ribonucleic acid

TBDMS= tert-butyl-dimethylsilyl

TEC= thiol-ene coupling

1. Introduction

The nucleoside, and nucleic acid analogues have significant therapeutic potential. In our work, we have synthesized new compounds by coupling cysteine to nucleosides, which can be oligomerized to produce novel peptide-nucleic acids, and also have interesting biological properties in their monomeric form. Different strategies were developed for the synthesis of the monomers and these methods were applied on 2 complementary nucleosides: adenine and uridine, and oligopeptides were obtained as well.

The photoinduced thioladdition is an advantageous reaction, which is widely used in the „click" chemistry, in chemical biology and carbohydrate chemistry, but is has not been used in nucleoside chemistry. Numerous reaction conditions were investigated on various unsaturated nucleoside derivatives, and an interesting observation was made as to how the yields and selectivity of the reactions can be influenced. Numerous compounds with remarkable biological activities have been synthesized.

2. Literature overview

2.1. Natural nucleosides and nucleoside derivatives

Nucleosides and their derivatives have a wide range of biological functions. They take part in the signal transduction (cAMP, cGMP), in the energy storage of the cell (ATP, NADH), in the photosynthesis (NADPH), and there are nucleoside type secunder metabolites with antimicrobial activity (uridyl peptide antibiotics).

2.2. Natural nucleic acids

In natural nucleic acids, the nucleobases are connected to a sugar-phosphate backbone. Two main properties of the nucleic acids are: the base sequence, and the properties of the backbone, which - in natural nucleic acids- is a polianionic structure. Complementary nucleic acids can hybridize to each other, forming double stranded structures. Therefore the order of the bases determines that with what sequence nucleic acid can a given nucleic acid hybridise. Nucleic acids are divided into 2 main classes, based on their chemical structure and their biological functions. DNA stores the genetic information in the long run in the nucleus, while the RNA posesses a wider range of functions.

2.3. Synthetic nucleic acid analogues

Natural nucleic acids are sensitive to nuclease enzymes which limits their usability. Therefore, for therapy and for experiments, modified nucleic acid analogues are used. The modification can take place on the nucleobase, on the internucleotide bond, or on the sugar component. The main goal is to increase the halflife of the molecule, but the improvement of the cellular uptake and the triplex formation ability and the RNase H activator effect are also important. These modifications can be combined. Most important types are the phosphorotioate nucleic acids, the LNA-s, the 2'-O-alkylsubstituted derivatives and the peptide nucleic acids.

2.4. Peptide nucleic acids

Peptide nucleic acids (PNA) were developed by Nielsen et al in 1991. In the original PNAs, the polyanionic sugar-phosphate backbone of natural nucleic acids has been changed to acyclic, electrically neutral oligo *N*-(2-aminoethyl)-glycine (AegPNA), in which, amide linkage was established between the amino group of the aminoethyl, and the carboxyl group of the next monomer, while nucleobases are connected to the nitrogen of the glycine, through a methylenecarbonyl linker. Since then, a lot of other variants were investigated, including derivatives which contain the whole nucleoside, not only the nucleobase (PRNA). The PNA backbone is achiral, acyclic, electrically neutral, and it does not contain the sugar moiety. These changes have definit advantages: because of the lack of the electric repulsion between the anionic nuclec acid and the PNA, the PNAs can excellenty hibrydise to DNAs and RNAs, forming very stable duplexes with high selectivity. PNAs are also resistant to nucleases and peptidases. They are not sensitive to acids and weak bases, which is advantageous for synthesis.

2.5. Nucleoside analogue drugs

Because of the wide range of biological roles of natural nucleosides, synthetic nucleoside derivatives can be used in several area of medicine. The compounds, which show structural similarity to natural nucleosides, can interact with the nucleoside recognising enzymes, and inhibit their activity, or incorporate into nucleic acids. For experimentals, a lot of different nucleoside analogues were synthesized with a high variety of biological effects. For clinical use, antitumor (trifluridine, cytarabine, 5-fluoruracile etc.) and antiviral derivatives (including the anticoronaviral favipiravir and remdesivir) are important.

2.6. Thiol addition

During my PhD work, the thiol addition, also known as thiol-ene coupling (TEC), was the most important synthetic method, so i would like to survey the characteristics of this reaction.

Thiol addition is one of the so called „click reactions”. These reactions can be executed quickly and simply with good yield, excellent selectivity and atom economy, they are compatible with wide range of reactants and reagents, and can be performed in any solvent. The TEC reactions can be divided into 2 main classes: Michael addition of thiols onto double bond through a thiolate, and radical addition, resulting in an anti-Markovnikov product. During my PhD work, I used the latter, so I will present the second one.

During the radical reaction, an initiator molecula generates a thiyl radical from the thiol. The electrophilic tiyl radical adds to the double bond, forming a carbon radical, which abstracts hydrogen from another thiol, and the cycle starts again. Termination step can be the recombination of two thiyl radicals into a disulfide. The reaction of the thiyl radical and the alkene is fast and reversible. The equilibrium depends on the electron density of the double bond, the stability of the carbon-centered radical and the reaction conditions. The hydrogen abstraction by the carbon radical must be faster than

its degradation. In the case of the photoactivated reactions, electromagnetic radiation leads to the homolytic cleavage of the initiator. The 2,2-dimethoxy-2-phenylacetophenone (DPAP) forms radicals under UV light irradiation. The photoredox methods are also popular, in which, photocatalysts are used to oxidise the thiol into a radical cation, from which the thyil is obtained by deprotonation, while the catalyst is regenerated (for example by the reaction with oxygen). Beside metal catalysts (e.g. tris-(bipyridine)-ruthenium-II-chloride or TiO_2) organocatalysts, for example 9-mesityl-10-methylacridinium salts, or rose bengal are more and more frequently used.

Thiol addition is widely used in synthetic chemistry, because of the wide range of applicable thiol and alkene partners and solvents. It is used in the polymer and carbohydrate chemistry for synthesize glycoconjugates or thiosugars. Additions have already been performed onto endo- and exocyclic double bonds of sugars with different thiols, including aliphatic and aromatic thiols, thiosugars and mercaptoalcohols. In the case of endoglycals, the yield and stereoselectivity depend on the structure of the alkene. From 2-substituated endoglycals, 1,2-cis-alpha thioglycosides can be obtained with excellent selectivity. Both the addition of the thiyl radical and the hydrogen abstraction are preferred from the axial direction (trans diaxial reaction), and are dependent on the conformation of the alkene, therefore, the stereoselectivity can be influenced by the reaction conditions, e.g. the temperature or the solvent, because these can influence the conformation of the alkene.

3. Goals

The goal of my PhD work was the synthesis of new, modified nucleoside derivatives via thiol addition that can be involved into biological experiments (e.g. cell viability or antiviral assays) and that also can be oligomerised into a new type of PNAs.

4. Methods

The reactions were monitored by TLC. The products were purified using flash column chromatography. The structures of the compounds were determined by one- and two-dimensional ^{1}H, ^{13}C, COSY and HSQC NMR measurements, as well as MALDI-ToF and ESI MS measurements. Optical rotations were measured at room temperature with an automatic polarimeter.

The photoinitiated reactions were carried out in a borosilicate flask by irradiation with a mercury lamp giving maximum emission at 365 nm. The lamp was covered with a water cooling immersion coating. The samples were placed up to 2 cm from the lamp. The samples were not bubbled through with inert gas and were not stirred during the irradiation steps. Low temperatures were achieved by immersing the samples into a liquid nitrogen-acetone cooling bath.

5. New scientific results

5.1. Addition of thiols to nucleosides

Although photoinitiated thiol-ene addition is widely used in carbohydrate chemistry, no one investigated this reaction on unsaturated nucleosides. I investigated the scope and limitations of the TEC reactions of nucleosides, and optimised the reaction conditions. A compound library was generated from sugar-modified nucleosides and several of the new compounds were involved in biological experiments (cell viability, antiviral, antibacterial and antimalarial studies).

5.1.1. Thioladditions of uridine and ribothymidine

I synthesized protected exomethylene derivatives from uridine and ribothymidine, and investigated their thiol-ene coupling reactions.

5.1.1.1. Thiol-ene additions of uridine and ribothymidine 4'-exomethylenes

Addition of *n*-propylmercaptane was tested on the 4'-exomethylene, obtained from uridine. Based on literature results, good yield and full D-*ribo* selectivity were expected. However, only 60% yield was obtained with 3 eq. of thiol, and the D-*ribo* and L-*lyxo* ratio was 2:1. Other initiation methods were investigated, but the yields were inferior to the photoinitiated one. The AIBN-initiated reaction was carried out at 120 °C, because the AIBN is thermally cleavable. In this case, 1.5:1 D-*ribo:*L-*lyxo* ratio was observed suggesting that the higher temperature decreases the selectivity. In parallel with my work, experiments with pyranosyl endoglycals were performed in our Department, which showed, that cooling can significantly increas the conversion. Therefore we studied the same reaction at lower temperatures. At -30 °C, 88% yield was obtained under photoinitiated conditions by using only two eq. of thiol. Also the ratio of the *ribo* isomer was doubled. At -80 °C, 5:1 ratio was obtained with similar yield.

After optimising the reaction conditions, the best conditions were applied in the other reactions. Uridine 4'-exomethylene was reacted under photoinitiated conditions at -80 °C with different thiols, including alkylthiols, amino acid derivatives and thiosugars. With primary thiols, good to excellent yields and stereoselectivities were obtained and always the *ribo* isomer was the main product. In case of the *t*-butyl-mercaptane, the ratio of the *lyxo* isomer was increased by cooling, which resulted the dercreasing of the selectivity (from 3:1 *ribo:lyxo* ratio to 2:1). In case of the 1-thiosugars, the selectivity depended on the configuration of the thiols. With 1-thiomannose, the reaction showed D-*ribo* selectivity, while with thiosugars with *gluco*- and *galacto* configurations, L-*lyxo* selectivity was observed. In the case of the additions of the ribothymidine 4'-exomethylenes, there was no significant difference from the analogous reactions of the uridine derivative.

5.1.1.2. Reactions of uridine and ribothymidine 3'-exomethylenes

Exomethylene group was formed at the 3'-position of the 2',5'-di-O-silyl ether protected uridine and ribothymidine. Based on the above mentioned experiences of the 4'-exomethylenes, the first

reactions were carried out at -80 °C. In the case of the simple alkyl thiols, the reactivity decreased with the increase of the length of the alkyl chain, possibly because of the higher electron donating capability of the alkyl chain, which can stabilize the electrophilic thiyl radical. Therefore, very low or no conversion was observed at -80 °C. However, the reactions of *n*-butyl-mercaptane revealed, that the high temperature decrease the selectivity (-80 °C: no conversion, -40 °C: 62% yield and 20:1 D-*xylo*:D-*ribo* ratio, while at 0 °C, the yield was not increased significantly, but the stereoselectivity was halved). In the case of the longest octyl and dodecyl mercaptanes, low yields were obtained even at 0 °C. Thioacetic acid showed low reactivity (26% yield at 0 °C), perhaps because of the acidity of the thiol which causes deprotonation instead of radical formation

Thiol additions onto the 3'-exomethylenes showed higher selectivity than the 4'-derivatives at room temperature and at low temperature, too. Suprisingly, in every cases, the corresponding D-*xylo* isomer was the major product. It is interesting because complete D-*gluco* selectivity for hydrothiolation of glucofuranose-3-exomethylene has been described in the literature. On the other hand, the additions of 1-thiosugars onto the 4'-exomethylenes showed opposite selectivity than the reactions of the primary thiols. In the reactions of the 3'-exomethylenes, there was no opposite selectivity observed, in every cases the D-*xylo* isomer was the main product. Therefore this reaction can be applied e to synthesize 3'-modified nucleoside derivatives with unnatural D-*xylo* configuration.

Several 3'-modofied xylofuranosyl nucleosides were involved in cell viability assay at the Department of Biotechnology and Microbiology on healthy HaCaT and tumorous SCC cell lines. MTT tests revealed, that the derivatives bearing an alkyl chain show cytostatic effect in a range of 10-30 μM with modest selectivity toward the tumorous cells.

Broad spectrum antiviral tests were executed in the Rega Institute in Belgium. Some compounds showed excellent antiviral activity against vaccinia virus, yellow fever virus and human coronavirus 229E. The β-D-glucose- and α-D-mannose-containing compounds are especially important, because these are not cytotoxic. The Glc-bearing derivative has 8 μM EC_{50} value against human coronavirus 229E, while the mannose analogue was not effective against this virus, which suggests that the configuration of the sugar, connecting to the nucleoside, is essential for the antiviral activity.

5.1.1.1.3. TEC-reactions of uridine and ribothymidine 2'-exomethylenes

2'-Exomethylenes were synthesized from both 3,'5'-TBDMS protected and 3',5'-silylene acetal protected uridine and ribothymidine derivatives. In the first case, additions of simple alkyl thiols (PrSH, BuSH) and thiosugars showed excellent *arabino* selectivity at room temperature and at -80 °C. The additions onto the silylene acetal proected exomethylenes showed similar results, although in the case of the thiosugars, the selectivity was decreased. This means, that the protecting groups of the alkene can also influence the stereoselectivity.

5.1.2. Reactions of adenosine exomethylene

Several reactions were also executed on the 2',3'-isopropylidene protected adenosine 4'-exomethylene, in this part, the addition of 1-thioglucose-peracetate is described. Under photoinitiated conditions, at -80 °C, the D-*ribo:*L-*lyxo* ratio was 1:3, just as in the case of the analogue uridine derivative. The obtained compound showed excellent effect against Plasmodium (66,15 nM IC_{50} value against Pf3D7).

5.2. Synthesis of cysteinyl nucleic acids

One of the main goals of my PhD work was the synthesis of nucleoside derivatives, which can be oligomerised into novel peptide nucleic acids. We planned to synthesize amino acid conjugates which can be oligomerised by peptide synthesis. To synthesize the monomers, it was necessary to produce the poperly protected nucleoside and amino acid derivatives, then to conjugate them. Because of the thiol group of the cysteine, the thioladdition is a suitable method. Another method is the nucleophilic substitution of nucleosides containing a 5'-leaving group. Both approaches were studied and their scope and limitatons were compared.

5.2.1. Synthesis of cysteinyl-uridine monomers via thiol addition

N-acetylcysteine and Fmoc-cysteine were involved in the experiments. Fmoc is a commonly used protecting group in the peptide chemistry, because it is cleavable under mild conditions. The reactions were carried out at -80 °C, and in both cases, excellent yield and selectivity were observed. The obtained Fmoc-protected compound is suitable for peptide synthesis, but the otherwise remarkable 91% isomer purity was not enough for this use.

5.2.2. Synthesis of cysteinyl-adenosine monomers via thioladdition

Cysteinyl-adenosine was planned to be synthesized from the isopropylidene protected 4'-exomethylene like the uridine analogue. But under the same conditions, the *ribo: lyxo* ratio was only 2:1, which suggests that the nucleobase can influence the selectivity considerably. We had to find another method to obtain the cysteinyl-adenosine monomer.

5.2.3. Synthesis of cysteinyl-adenosine and uridine monomers via nucleophylic substitution

Another potential method to synthesize cysteinyl-nucleosides is nucleophilic substitution. For this, 5'-activated nucleosides were prepared.

2',3'-TBDMS, or isopropylidene protected 5'-iodo derivatives were synthesized from uridine and were coupled to protected cysteine derivatives. Then, the obtained C-terminal and N-terminal monomers were coupled into dipeptides. 2',3'-*O*-isopropylidene *N*-Fmoc protected monomer was also obtained, which was used for solid-phase peptide synthesis (SPPS).

5'-Iodoadenosine was synthesized and subjedted to nucleophilic substitution reaction with cysteine derivatives. Unfortunately, under mild conditions (Cs_2CO_3, 0 °C), no conversion occurred,

while under harsch conditions (NaOH, 80 °C), only degradation products were isolated. Therefore, the nucleophilic substitution proved to be inappropriate for the synthesis of cysteinyl-adenosine monomers.

5.2.4. Synthesis of homonucleoside monomers from uridine, adenosine and cytidine

Since the nucleophilic substitution requires too harsch conditions, while the thiol addition does not show sufficient stereoselectivity, a new method was investigated to produce cysteinyl monomers. The protected uridine, adenosine and cytidine derivatives were oxidised into 5'-aldehyde, then Wittig olefination was used to obtain 5'-6'-unsaturated derivatives. With these compounds, thiol addition can be performed under mild conditions, and since no new chiral center is formed during the reaction there are no selectivity problems. Unfortunately, in these cases, the yields were lower than in the reactions of the 4'-exomethylenes, and only a moderate increase was achieved by changing the reaction conditions.

5.2.5. Dimerisation and oligomerisation reactions

Dimers were synthesized from the properly protected C-, and N-terminal monomers by liquid-phase synthesis. From uridine, a TBDMS protected homodimer was obtained. From the chain-elongated monomers, hUhU, hAhA and hAhU dimers were prepared.

A longer oligomer was also synthetsized by solid phase peptide synthesis. Since high excess of monomer is required for the effective coupling steps, the amount of the isopropylidene and Fmoc protected monomer was enough for a pentapeptide. The solid phase was Wang resin, the coupling agents were DCC and HOBt. The product was cleaved from the resin and prepurified by flash chromatography and gel filtration. the final purification and characterisation was performed by HPLC chromatography.

5. Summary

The aim of my PhD work was the synthesis of potentially biologycally active new nucleoside derivatives. To achieve this goal, we have chosen the thiol-ene coupling as a synthetic tool. We performed radical mediated thiol additions onto nucleoside alkenes for the first time. The relationship between the stereoselectivity and the reaction conditions (temperature, solvent, initiation) and also the structure of the thiol or the alkene (including the role of the applied protecting groups or nucleobase) were investigated. Four nucleosides (uridine, adenine, ribothymidine, cytidine) were involved in the experiments, and dozens of novel 2'-, 3'- and 5'-modified nucleoside derivatives were obtained. After optimizing the reaction conditions, good to excellent yield and stereoselectivity was obtained in most of the cases. Cooling generally increased both the yield and the selectivity significantly. This method is well suited to synthesize new uridine and ribothymidine derivatives with unnatural D-*xylo*- and D-*arabino* configuration. These compounds were studied in biological assays by our cooperators. Among the 3'-modified compounds, the alkyl chain-containing ones have shown remerkable cytostatic activity, while some of the the sugar-containing derivatives were active against viruses. The adenosine derivatives have shown antimalarial activity.

In the synthesis of cysteine-nucleic acids (peptide-nucleic acids with completly new structure), the main problem was that the monomers, obtained by thiol addition, contained the diastereisomer as an impurity. Furthermore, the alternative nucleophilic substitution method did not work on every nucleosides. Finally, we could solve the problem by thiol-ene reactions of unsaturated homonucleosides. In this case, the yields were low, but could be increased by changing the reaction conditions. This method proved to be suitable to obtain cysteinyl derivatives from all investigated nucleosides. Several monomers were synthesized and also coupled into dipeptides. Finally, a pentapetide was obtained by SPPS, using conventional peptide chemistry methods.

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7. List of scientific publications

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List of publications related to the dissertation

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3. Kiss, A., Baksa, V., Tálas, L., **Bege, M.**, Borbás, A., Bereczki, I., Bánfalvi, G., Szemán-Nagy, G.: MTT Test and Time-lapse Microscopy to Evaluate the Antitumor Potential of Nucleoside Analogues.
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