SYNTHESIS OF NOVEL L-NUCLEOSIDES AS POTENTIAL ANTIVIRAL AND ANTITUMOR AGENTS

(PhD Thesis)

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Thesis subject, aims and theoretical background

The current arsenal of therapeutic compounds against viral infections is the result of several decades of research, including syntheses and biological test of nucleosides and nucleoside analogues. [1] Although the synthesis of the first L-nucleoside was published in 1964 until the discovery of lamivudine (anti-HIV and anti-HBV agent) no widespread synthetic interest had been associated with the preparation of the L-form of the nucleosides. Afterward a great number of L-nucleoside analogues have been synthesized and tested for antiviral activities. Most L-enantiomers considered for treating virus diseases have similar activities to their D-counterparts, but are less sensitive to degrading enzymes and have better safety profiles. However, therapeutic potential of L-nucleosides is not restricted exclusively to their antiviral mode of action and for example L-adenosine and L-thymidine posses anti-malaria while troxacitabine has anticancer activity against pancreatic tumor and myeloid leukemia.

Based on the structure-activity relationship studies revealed for D-nucleosides, our experimental objectives were to synthesize new L-analogues with potential antiviral and anticancer activities. Assembly of two molecule libraries has been envisaged by modification of pirimidine bases at position 5 as well as by 2'-substitution of the sugar (L-ribose) moiety. One of these libraries includes 5-halo, 5-thienyl and 5-(5-halonthien-2-yl)-*ara*-L-uridines as well as the corresponding cytidine derivatives. While the other library comprises 2'-position modified *ribo*-configured L-nucleosides such as 2'-deoxy-2'-(halogeno or azido)-L-uridines and their 5-iodo as well as 5-thienyl derivatives. Further objectives were to evaluate the cytotoxic and antiviral activity of new molecules prepared and to investigate the effect of base and sugar moiety modifications on the biological activities. In additon, we also planned the preparation of diphosphates such as L-adenosine- and L-cytidine-5'-diphosphates as model compounds for the study of substrate specificity of PGK (3-phosphoglycerate kinase) enzyme in the frame a cooperation research.

Methods applied

Both macro- and semi-micro methods of preparative organic chemistry were used throughout this research. Proceedings of the reactions were followe by thin-layer chromatography, and products of the reactions were purified by silica gel chromatography. In addition to classical analytical techniques such as melting point and optical density measurements, mass

spectrometry, 1D- and 2D-NMR spectroscopy such as ^{1}H-, ^{13}C- and ^{19}F-NMR, HSQC were used. Cytotoxicity of the molecules was evaluated by MTT test, while antiviral properties of the molecule were studied with cytopathic effects (CPE).

New scientific results of the dissertation

1. Preparation of new 5-halo-*ara*-L-uridines

Preparation of *ara*- és a *ribo*-configured L-uridines was carried by the modification of method by Holy et al.[2] (Fig. 1). Condensation of **1** anhydro derivative prepared from L-arabinose and cyanamide with methyl propiolate offered 2,2'-anhydro-L-uridine (**2**, 63%). Derivative **2** is a key intermediate in our synthetic approach since it serves as starting material in the synthesis of both *ara*- and *ribo*-derivatives. *ara*-L-Uridine (**3**, 98%) was prepared in a base-mediated ring-opening reaction from compound **2**. The *ribo*-configured L-uridines (**40**) were obtained from **35** benzoyl-protected derivative of intermediate **2** in Lewis acid-catalyzed isomerisation (70%).

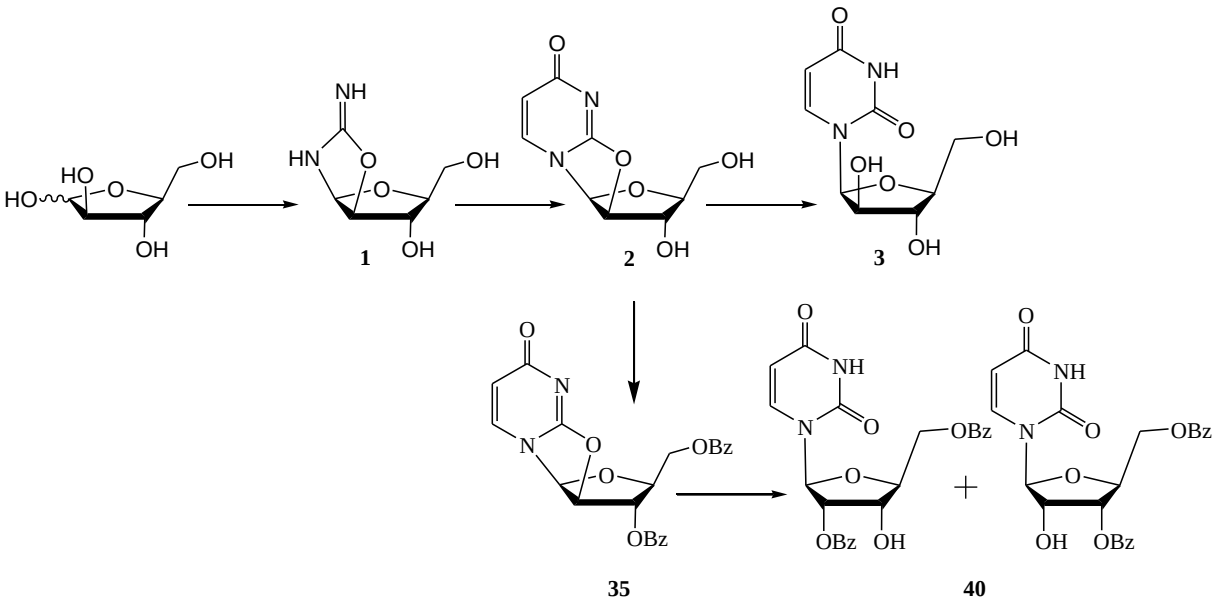


Figure 1. *Preparation of ara- and ribo-configured L-nucleosides from L-arabinose.*

Synthetic procedure for the preparation of 5-halo-L-uridines was summarized on Fig. 2. The 2',3',5'-tri-*O*-benzoyl-*ara*-L-uridine (**4**) obtained by benzoylation of *ara*-L-uridine (**3**) was also a starting material during the synthesis of 5-halogen modified derivatives. The benzoyl-protected 5-chloro derivative (**5**) was prepared from compound **4** in halogenation reaction with ceric ammonium nitrate (CAN) and lithium chloride (87%). Under similar conditions

with lithium bromide **7** protected 5-bromo derivative (88%) was prepared from **4**. The 5-iodo compound (**9**, 97%) was obtained in the reaction of **4** and NIS reagent. Zemplen debenzoylation of these 5-halo compounds provided the new 5-chloro- (**6**, 81%), 5-bromo- (**8**, 85%) and 5-iodo-*ara*-L-uridines (**10**, 89%).

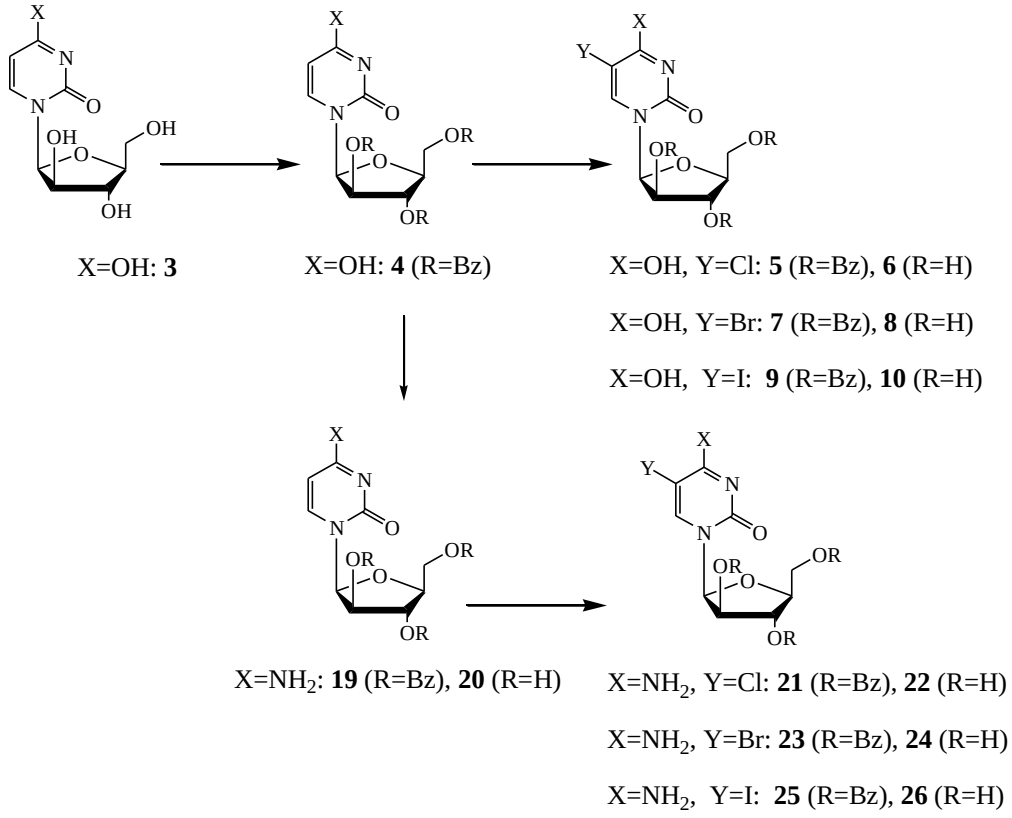


Figure 2. *Preparation of 5-(chloro, bromo, iodo)-ara-L-uridines and cytidines.*

2. Preparation of 5-(thien-2-yl)- and 5-(5-halo-thien-2-yl)-*ara*-L-uridines

Preparation of 5-(thien-2-yl)- and 5-(5-halo-thien-2-yl)-*ara*-L-uridines is outlined on Fig. 3. The benzoyl-protected 5-(thien-2-yl)-*ara*-L-uridine (**11**) was synthesized from 5-iodo-2',3',5'-tri-*O*-benzoyl-*ara*-L-uridine (**9**) and tributylstannyl tiophene in Stille cross-coupling reaction[4] (64%). From **11** thienyl derivatives halogenation with NCS provided the protected 5-chloro derivative (**13**, 90%), halogenation with bromine offered the protected 5-bromo derivative (**15**, 92%) while halogenation with NIS afforded the protected 5-iodo derivative (**17**, 97%). Four new L-uridines such as 5-(thien-2-yl)- (**12**, 86%), 5-(5-chloro-thien-2-yl)- (**14**, 79%), 5-(5-bromo-thien-2-yl)- (**16**, 89%) and 5-(5-iodo-thien-2-yl)-*ara*-L-uridine (**18**, 50%) was then obtained by debenzoylation of intermediates **11**, **13**, **15** and **17**.

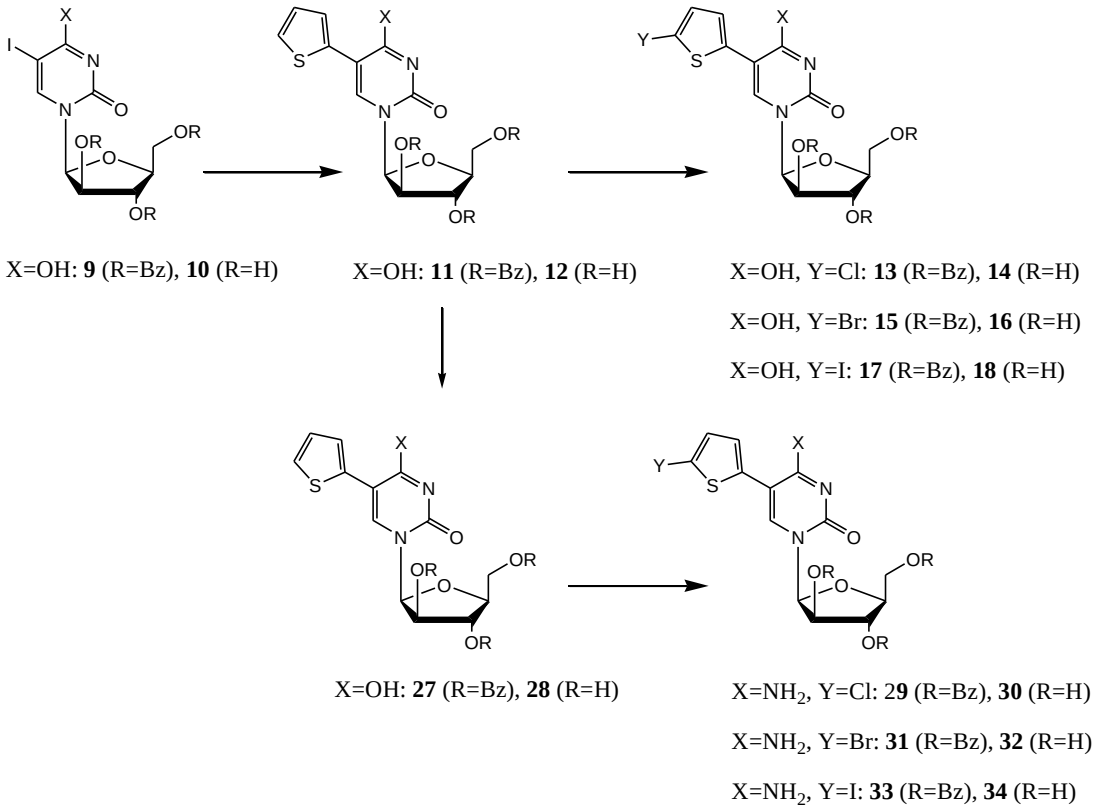


Figure 3. *Preparation of 5-(thien-2-yl) as well as 5-(5-(chloro, bromo, iodo)-thien-2-yl)-ara-L-uridines and cytidines.*

2. Preparation of 5-halogeno-*ara*-L-cytidines

During the synthesis of 5-halogeno-*ara*-L-cytidines (Fig. 2) 2',3',5'-tri-*O*-benzoyl-*ara*-L-cytidine (**19**, 70%) was prepared from a 2',3',5'-tri-*O*-benzoyl-*ara*-L-uridine (**4**) via 4-(1,2,4-triazol-1-yl)- 2',3',5'-tri-*O*-benzoyl-*ara*-L-uridine by ammonolysis. The L-cytidine derivative (**19**) halogenation was accomplished with NCS to obtain the protected 5-chloro derivative (**21**, 94%), with bromine to obtain the protected 5-bromo derivative (**23**, 82%) and with NIS to get 5-iodo derivative (**25**, 77%). Zemplen debenzoylation of these halo derivatives and compound **4** afforded the new 5-chloro- (**22**, 82%), 5-bromo- (**24**, 91%) and 5-iodo-*ara*-L-cytidine (**26**, 86%), as well as the known *ara*-L-cytidine (**20**, 86%).

4. Preparation of 5-(thien-2-yl)- and 5-(5-halo-thien-2-yl)-*ara*-L-cytidines

Synthesis of 5-(thien-2-yl)- and 5-(5-halo-thien-2-yl)-*ara*-L-cytidines is outlined on Fig. 3. The 5-(thien-2-yl)-2',3',5'-tri-*O*-benzoil-*ara*-L-cytidine (**27**, 57%) was prepared from 5-(thien-2-yl)-2',3',5'-tri-*O*-benzoyl-*ara*-L-uridine (**11**) via the 4-(1,2,4-triazol-1-yl)-5-(thien-2-yl)-2',3',5'-tri-*O*-benzoyl-*ara*-L-uridine intermediate by ammonolysis. Halogenation of **27**

compound with NCS offered the protected 5-chloro product (**29**, 81%), with NBS provided 5-bromo product (**31**, 91%), while with NIS gave 5-iodo derivative (**33**, 61%). Zemplen debenzoylation of compound **27** and these halo derivatives four new L-nucleosides such as 5-(htien-2-yl)- (**28**, 81%), 5-(5-chloro-thien-2-yl)- (**30**, 79%), 5-(5-bromo-thien-2-yl)- (**32**, 78%) and 5-(5-iodo-thien-2-yl)-*ara*-L-uridine (**34**, 39%) were obtained.

5. Preparation of 5-(iodo, thienyl)-2,2'-anhydro-L-uridines

Ouline of the synthesis of base-modified 2,2'-anhydro-L-uridines is shown on Fig. 4.

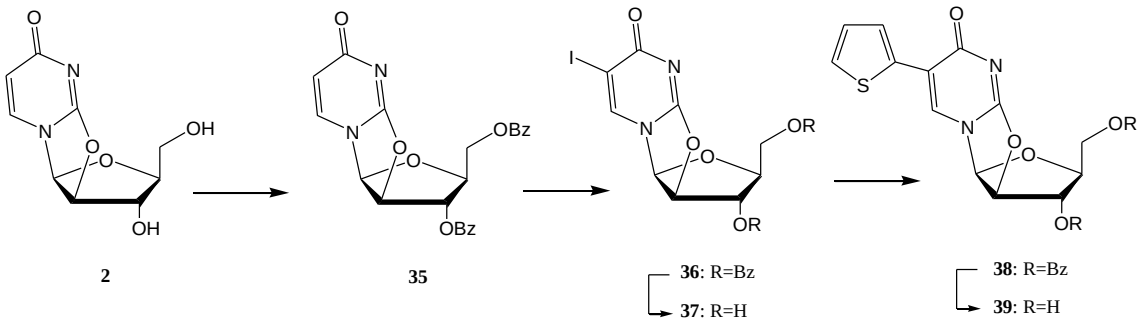


Figure 4. *Preparation of 5-iodo- and 5-thienyl-anhydro-L-uridines.*

The iodination of benzoyl-protected 2,2'-anhydro-L-uridine (**35**) carried out with NIS in TFA-DCE solvents provided the protected 5-iodo derivative (**36**, 78%) from which the protected 5-thienyl compound (**38**) was obtained in Stille cross-coupling reaction (61%). Removal of protecting group from intermediates **36** and **38** by Zemplen debenzoylation yielded two new nucleosides such as 5-iodo-2,2'-anhydro- (**37**, 64%) és az 5-thienyl-2,2'-anhydro-L-uridine (**39**, 88%).

6. Preparation of 5-(iodo and thienyl)-L-uridines

Mixture of **40** dibenzoyl compounds was prepared from 3',5'-di-*O*-benzoyl-2,2'-anhydro-L-uridine (**35**) in an isomerisation reaction catalyzed by boron trifluoride etherate[5] (Fig. 1., 99%). The mixture of dibenzoyl uridines served as starting material for the synthesis of base-modified L-uridines (Fig. 5).

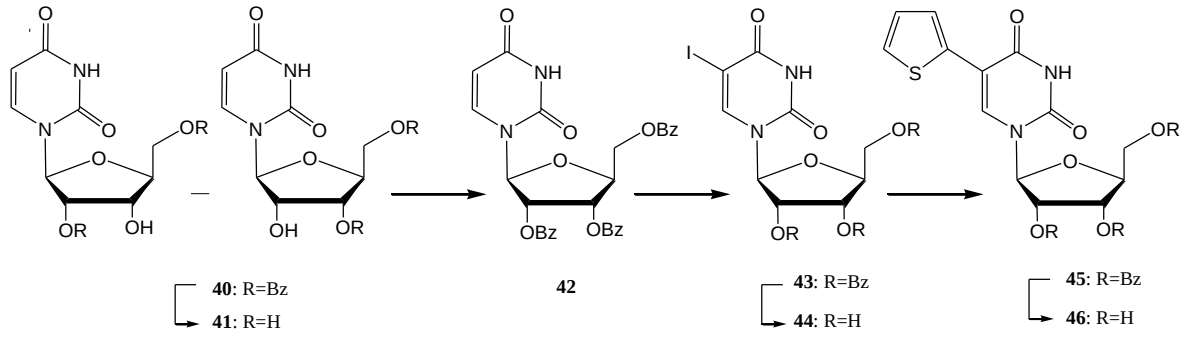
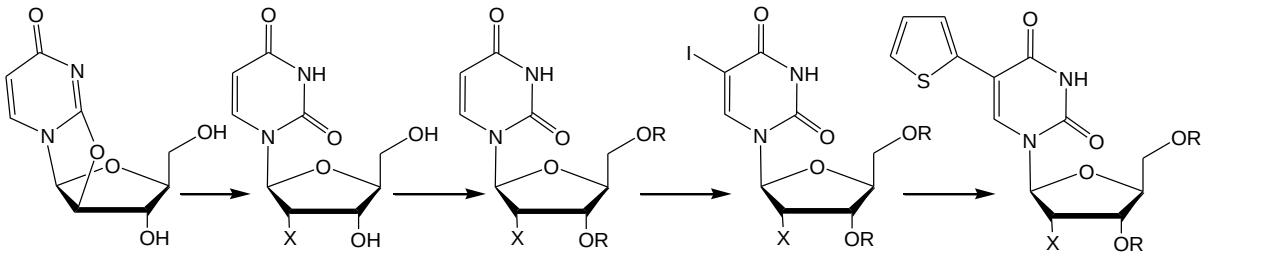


Figure 5. *Preparation of L-uridine as well as 5-iodo- and 5-thienyl-L-uridines.*

Benzoylation of **40** dibenzoyl derivatives followed by iodination of the product 2',3',5'-tri-*O*-benzoyl-*ribo*-L-uridine (**42**) with NIS reagent provided the protected 5-iodo-L-uridine (**43**, 96%). Stille coupling of this iodo intermediate with tributylstannyl thiophene resulted in the protected 5-(thien-2-yl)-L-uridine (**45**, 75%). Finally Zemplen deacetylation of compounds **40**, **43** and **45** provided a new **46** (87%) and two known derivatives (**41**, 77%; **44**, 89%).

7. Preparation of 5-(iodo and thienyl)-2'-deoxy-2'-azido-L-uridines

During the synthesis of base-modified 2'-deoxy-2'-azido-L-uridines (Fig. 6) the unknown 2'-deoxy-2'-azido-L-uridine (**47**) was prepared in the reaction of intermediate 2,2'-anhydro-L-uridine (**2**) and lithium azide with moderate yield (41%).[6] Benzoylation of **47** followed by iodination of the **48** product with NIS resulted in the protected 5-iodo derivative (**49**, 95%). Sille coupling of this product with tributylstannyl thiophene resulted in the protected 5-thienyl compound (**51**, 54%). Debenzoylation of **49** and **51** intermediates yielded the new 5-iodo-2'-deoxy-2'-azido-L-uridine (**50**, 78%) and 5-(thien-2-yl)-2'-deoxy-2'-azido-L-uridine (**52**, %)



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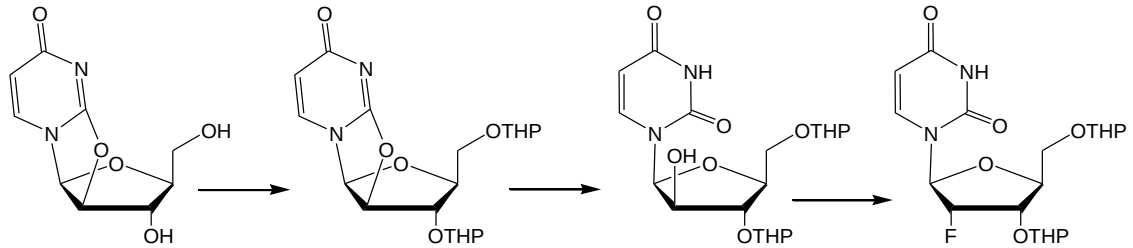
X=N_3: **47**	**X**=N_3: **48** (R=Bz)	X=N_3: **49** (R=Bz), **50** (R=H)	X=N_3: **51** (R=Bz), **52** (R=H)
X=F: **56**	**X**=F: **57** (R=Bz)	X=F: **58** (R=Bz), **59** (R=H)	X=F: **60** (R=Bz), **61** (R=H)
X=Cl: **62**	**X**=Cl: **63** (R=Bz)	X=Cl: **64** (R=Bz), **65** (R=H)	X=Cl: **66** (R=Bz), **67** (R=H)
X=Br: **68**	**X**=Br: **69**(R=Bz)	X=Br: **70** (R=Bz), **71** (R=H)	X=Br: **72** (R=Bz), **73** (R=H)

Figure 8. *Preparation of 2'-deoxy-2'-(azido, fluoro, chloro, bromo, iodo)-L-uridines as well as their 5-iodo- és 5-thienyl derivatives.*

8. Preparation of 5-(iodo and thienyl)-2'-deoxy-2'-fluoro-L-uridines

During the synthesis of tetrahydropyranyl-protected 2'-deoxy-2'-fluoro-L-uridine (**55**, Fig. 7) the THP protection of hydroxy groups of 2'-anhydro-L-uridine (**2**) yielded **53** THP-ether from which alkaline hydrolysis offered the protected *ara*-L-uridine (**54**, 96%). Fluorination of **54** with DAST[7] followed by cleavage of THP groups of 3',5'-di-*O*-tetrahydropiranyl-2'-deoxy-2'fluoro-L-uridine (**55**) resulted in the product 2'-deoxy-2'-fluoro-L-uridine (**56**, 84%).



2 **53** **54** **55**

Figure 7. *Preparation of 2'-deoxy-2'-fluoro-3',5'-di-tetrahiydropiranyl-L-uridine.*

The preparation of 5-iodo- as well as 5-thienyl-2'-deoxy-2'-fluoro-L-uridines is outlined on Fig. 6. Iodination of the benzoyl-protected **57** with NIS yielded the 5-iodo derivative (**58**, 95%) which was coupled with tributylstannyl thiophene to give the Stille product 5-iodo derivative (**60**, 91%). Debenzoylation of compounds **58** and **60** provided the known 5-iodo-2'-deoxy-2'-fluoro-L-uridine (**59**, 88%) and a novel 5-(thien-2-yl)-2'-deoxy-2'-fluoro-L-uridine (**61**, 89%)

9. Preparation of 5-(iodo and thienyl)-2'deoxy-2'-chloro-L-uridines

During the synthesis of base-modified 2'-deoxy-2'-chloro-L-uridines (Fig. 6) initially 2'-deoxy-2'-chloro-L-uridine (**62**) was prepared in the reaction of 2,2'-anhydro-L-uridin (**2**) and HCl in DMF[6]. Benzoylation of **62** yielded the benzoyl-protected **63** which was iodinated with NIS in TFA-DCE solvent mixture to give the protected 5-iodo derivative (**64**, 98%). The Stille coupling of iodo compound with tributylstannyl thiophene resulted in **66** protected 5-thienyl derivative (94%). Finally, Zemplen deacetylation of **64** and **66** yielded two novel L-uridines such as 5-iodo-2'-deoxy-2'-chloro- (**65**, 67%) and 5-thienyl-2'-deoxy-2'-chloro-L-uridine (**67**, 67%).

10. Preparation of 5-(iodo and thienyl)-2'-deoxy-2'-bromo-L-uridines

2'-Deoxy-2'-bromo-L-uridine (**68**) the intermediate of the synthesis of base-modified 2'-deoxy-2'-bromo-L-uridine derivatives (Fig. 6) was obtained in the reaction of 2,2'-anhydro-L-uridine (**2**) and HBr-acetic acid.[6] Benzoylation of **68** bromo compound followed by iodination of **69** protected nucleoside with NIS yielded the protected 5-iodo-2'-bromo-L-uridine (**70**, 80%). Stille coupling of this 5-iodo derivative with tributylstannyl thiophene provided the protected 5-thienyl-2'-bromo-L-uridine (**72**, 82%). Deprotection of **70** and **72** by Zemplen deacetylation resulted in novel 5-iodo-2'-deoxy-2'-bromo- (**71**, 81%) and 5-thienyl-2'-deoxy-2'-bromo-L-uridine (**73**, 37%).

11. Preparation and purification of L-cyitidine- and L-adenosine-5'-*O*-diphosphates

The protected L-cytidine and L-adenosine derivatives were prepared from 1-*O*-acetyl-2',3',5'-tri-*O*-benzoyl-L-ribofuranoside and the respective nucleobase (cytosine, N^6-benzoyl-adenosine by the Vorbrüggen method[8]. The yields however were inferior (70 and 19%) to those reported (96% and 93%). The preparation of monophosphates was accomplished by Yoshikawa's method[9] while the synthesis of diphosphates was carried out using the protocol of Gondeau et al.[10] Nevertheless, monophosphates could be isolated in greater yields (L-CMP, 81%) than yields reported[10] (L-CMP, 48%) due to the purification procedure developed in our laboratory. According to this method the solid mixture of the product and inorganic salts was dissolved in water and the pH was adjusted to 2 by 1N HCl and this solution was applied to a Dowex 50W H8 H^+ ion-exchange column. Inorganic components such were eluted with water while the respective phosphates were eluted with concentrated NH_4OH to yield the

ammonium salt of the phosphates. The advantage of this method that it can be applied for the purification of nucleoside phosphates containing amino group on the nucleic base.

12. Cytotoxicity studies with the compounds of the two L-nucleoside libraries

The sugar- and base-modified L-nucleosides were tested on four cancer cell line such as Hel, HeLa, Vero, and MDCK while the base-modified ara-L-nucleosides were subjected to *in vitro* cytotoxicity studies with L1210 cell line in addition to the aforementioned cell lines. Of the L-nucleosides studied only compound **12** was cytotoxic (HEL: EC_{50}, 0.8 µM and HeLa: EC_{50}, 20 µM). On MDCK cell line also compound **12** showed the highest cytotoxicity (EC_{50}, 20 µM) and the majority of L-nucleosides were effective only at concentration of 100 µM. According to the results of studies on L1210 cell line the *ara*-L-uridin (**3**) was only slightly cytotoxic and the activity of its 5-halo derivatives (**6**, **8**, **10**) were less effective molecules possessing EC_{50} values at over 200 µM of concentration. Meanwhile the 5-(2-thienyl)-*ara*-L-uridine (**12**) exhibited also remarkable cytotoxicity (EC_{50}, 13.8 µM), however the same base-modified *ara*-L-cytidine (**28**) was inactive in this test. Of the 5-(5-halothien-2-yl)-*ara*-L-uridine derivatives only the chloro (**14**) and iodo (**18**) compounds were cytotoxic and the bromo (16) compound was ineffective. Of the 5-(5-halothien-2-yl)-*ara*-L-cytidine derivatives only the chloro (**30**) exhibited remarkable cytotoxicity (EC_{50}, 37.6 µM). Of the all tested compounds overall three L-nucleosides such as **12**, **14**, **30** exhibited $EC_{50} < 50$ µM cytotoxicity value. The 5-(2-thienyl)-*ara*-L-uridin (**12**) was cytotoxic on all cell lines having most effective on Hel cell line (EC_{50}, 0.8 µM). Even though the most active **12** was less cytotoxic in a concentration of one order of magnitude than the reference standards it seems that further modifications on structure of **12** may enhance its cytoxicity.

13. Antiviral studies with the compounds of the two L-nucleoside libraries

Antiviral evaluations carried out with L-nucleosides on 14 virus strains such as herpes simplex-1 (KOS), herpes simplex-1 (TK^- KOS ACV^r), herpes simplex-2 (G), vaccinia virus, vesicular stomatitis virus, coxsackie virus B4, respiratory syncytal virus, parainfluenza-3 virus, reovirus-1, sindbis virus, punta toro, influenza A H1N1 subtype (A/PR/8), influenza A H3N2 subtype (A/HK/7/87) és influenza B (B/HK/5/72) virus in cytopathic effect assays (CPE) were performed by Rega Institute for Medical Research, Universiteit Leuven, Belgium. While the majority of the L-nucleosides were found ineffective on these virus strains, compound **71** showed marginal activity (EC_{50}, 100 µM) on herpes simplex-1 (KOS) strain. On respiratory syncytal strain eleven experimental L-nucleosides such as **2**, **10**, **16**, **34**, **37**, **44**,

47, **56**, **62**, **65**, **68** exhibited marginal antiviral activity (EC_{50}, 100 μM). On reovirus-1 and punta toro strains only 5-(2-thienyl)-*ara*-L-uridine (**12**) was active (EC_{50}, 100 μM) and this molecule showed higher activity (EC_{50}, 45 μM) on sindbis strain.

14. Results of enzyme kinetic studies

The substrate specificity of the PGK (3-phosphoglicerate kinase) enzyme was studied by *in vitro* enzyme kinetic assays and by *in silico* homology modelling experiments in comparision with the substrate specificity of piruvate kinase (PK) and creatine kinase (CK). The binding affinity studies confirmed the previously reported results that PGK can more efficiently phosphorylate the purin nucleosides than PK or CK. On the contrary, PK and CK much more active on the phosphorylation of pyrimidine nucleosides than PGK. Nevertheless, L-CDP was proved to be a better substrate of PGK than D-CDP. It was conluded that in contrast to PK and CK PGK can excellently tolerate the L-form of both purine or pyrimidine nucleosides.

Exploitation of the results and further objectives

Thirty-four L-nucleoside was synthesized in experiments and 24 of these compounds have been unknown in the literature. Although the majority of the molecules exhibited no cytotoxic and antiviral activity on the studied tumor cell lines and virus strains it would be worth evaluate their biological activity on HIV, hepatitis B and C strains since L-nucleosides have been known to be effective against these strains. Since 5-(2-thienyl)-*ara*-L-uridine (**12**) was shown as the most active molecule in both antitumor and antiviral tests the modification of its sugar moiety (halogen or azido substitution) looks reasonable to improve the bioactivity.

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