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

Synthesis of a novel heterotricycle containing nucleoside analogues

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The Examination takes place at the Library of Department of Pharmacology, Faculty of Pharmacy, University of Debrecen, on the 8th of May, 2018, at 11 am

Head of the **Defense Committee**:	Lajos Gergely, MD, PhD, DSc
Reviewers:	Loránd Kiss, PhD, DSc
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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on the 8th of May, 2018, at 1 pm

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List of abbreviations

^{1}H-^{13}C HMBC: proton-carbon heteronuclear multiple-bond correlation spectroscopy

^{1}H-^{13}C HSQC: proton-carbon heteronuclear single-quantum correlation spectroscopy

^{1}H-^{1}H COSY: proton-proton correlation spectroscopy

2D NMR: two-dimensional nuclear magnetic resonance

AIDS: acquired immune deficiency syndrome

ALL: acute lymphoblastic leukemia

AMD: age-related macular degeneration

AML: acute myeloid leukemia

CLL: chronic lymphocytic leukemia, B-cell chronic lymphocytic leukemia (B-CLL)

CML: chronic myelogenous leukemia

CMV: cytomegalovirus (HHV-5)

DFT: density functional theory

DMTr: 4,4'-dimethoxytrityl

DNA: deoxyribonucleic acid

ESI: electrospray ionization

FDA: Food and Drug Administration

Fmoc: fluorenylmethyloxycarbonyl

HHV: humán herpesvirus

HIV: human immunodeficiency virus

HTLV: human T-cell lymphotropic virus

LNA: locked nucleic acid

MALDI: matrix-assisted laser desorption ionization

MMTr: 4-monomethoxytrityl

NMR: nuclear magnetic resonance

PMO: phosphorodiamidate morpholino oligomer

RNA: ribonucleic acid

TBAF: tetra-*n*-butylammonium fluoride

TBDMS: *tert*-butyldimethylsilyl

TES: triethylsilyl

Tris: tris(hydroxymethyl)aminomethane

1. Review and aims of the dissertation

1.1. Literary review

1.1.1. Nucleoside and nucleotide analogue active substances

Nucleoside and nucleotide types of active substances used for therapeutical purposes operate various mechanisms of action. They can inhibit the cell proliferation at various points, for example: replication, transcription, translation or other biological function. The similarity in these molecules is that the carbohydrate moiety and/or the heterocyclic base are usually modified in these compounds. The modified derivatives are used either as a monomer or as an oligomer. These compounds are produced by means of chemical synthesis, granting an important role to the pharmaceutical chemists during the development of a new molecule.

The antineoplastic and immunosuppressive inhibitors of the biosynthesis of the nucleic acid are also known as antimetabolites. They can be activated in the organization by enzymes (phosphorylase, kinase) and can interact with the target, such as DNA polymerase or ribonucleotide reductase, or they can be incorporated into the DNA and/or RNA causing chain termination, ruption, or damage. Consequently, inhibiting cell proliferation will lead to cell death.

Based on their chemical structures, nucleoside and nucleotide analogue compounds are classified into two groups. The pyrimidine (tegafur, floxuridine, doxifluridine, capecitabine, 5-fluorouracil, cytarabine, gemcitabine, azacitidine and decitabine) or purine antagonists (6-mercaptopurien, 6-thioguanine, azathioprine, fludarabine phosphate, cladribine, pentostatin, clofarabine and nelarabine) are used in the treatment of many types of cancer, e.g., hairy cell leukemia, ALL, AML, CML, CLL, Hodgkin's and non-Hodgkin's lymphomas, breast, ovarian and pancreatic cancers, and non-small-cell lung carcinoma, as well as in immunosuppressive therapy of autoimmune inflammatory syndromes (Crohn's disease, ulcerative colitis, rheumatoid arthritis) and kidney transplantation.

Antiviral nucleoside and nucleotide analogue pharmacons can be grouped similarly to antineoplastic agents. Viral genom (DNA or RNA) and enzymes (polymerases, kinases, proteases, integrases) are known as their targets. Purine (aciclovir, valaciclovir, penciclovir, famciclovir, ganciclovir, valganciclovir, didanosine, abacavir, adefovir, adefovir dipivoxil, tenofovir, tenofovir disoproxil, entecavir, ribavirin, and viramidine) or pyrimidine analogues (zidovudine, stavudine, lamivudine, emtricitabine, idoxuridine, brivudine, trifluridine, epervudine, and cidofovir) are effective antivirals against variola virus, vaccinia virus, herpesviruses, papillomaviruses, hepatitis B and C viruses, rotavirus, rubeolavirus, flavivirus,

coronavirus, morbilli virus, mumps virus, influenzavirus, lyssavirus, Ebola and Marburg virus, poliovirus, retroviruses (HIV, HTLV), and rhinovirus.

1.1.2. Conformationally restricted nucleoside derivatives

The furanose ring is never planar in natural nucleosides, but it shows an envelope or half-chair conformation. This process is called puckering, which can manifest in several forms during the pseudorotation cycle. In most instances two main conformational states are balanced: C2'-*endo* (S-type, South-type) and C3'-*endo* (N-type, North-type). The N-type appears in ribonucleosides of A-RNA, while the S-type can be found in 2'-deoxyribonucleosides of the double helix forming B-DNA.

The different conformational states play a major role in the biological functions of the nucleosides. Capitalizing on these effects in the last two decades, different types of conformationally restricted nucleoside and nucleotide analogues were synthetized. Research in biology led to publishing several observations and results, e.g., enzymatical binding and stability, hybridization and stability of the duplex are influenced by the restricted conformation of the substitueted tetrahydrofuran formed from the furanose moiety. N-type of constrained conformation was formed by 2'-*O*,4'-*C*-CH_2-bridge in LNAs. β-D-LNA is archetype of the 2'-*heteroatom*,4'-*C*-bridged nucleosides, which was broadened with different derivatives (β-D-xylo-LNA, α-L-LNA, α-L-xylo-LNA, β-L-LNA, α-D-LNA, β-L-xylo-LNA, α-L-xylo-LNA, 2'-thio-β-D-LNA, 2'-amino-β-D-LNA, phosphorothioate-β-D-LNA, methylphosphonate-β-D-LNA) over time.

In vitro and *in vivo* properties of LNA derivatives incorporated into antisense oligonucleotides were studied in biological tests. The LNA containing oligonucleotides can serve as function as efficient antisense compounds, because they can bind to the complementer chain remarkably, they can block the RNA-processing enzymes, they can form triplexes, and they can result in a significant activation of RNase H. The results affirmed that the pharmacokinetic parameters can be arrestingly changed by choosing of suitable LNA chemistry.

Several bi- and tricyclic nucleoside analogues such as 2'-*O*,3'-*C*-CH_2-, 2'-*O*,3'-*C*-$(CH_2)_2$- and 3'-*C*,5'-*C*-$(CH_2)_2$-bridge or a 3,6,10-trioxatricyclo[$5.3.1.0^{2,11}$]undecane containing 2'-deoxyribo- and ribonucleoside derivatives were synthetized in order to restrict the conformation of carbohydrate moiety of nucleic acids to increase their biological stability. Since these compounds can be oligomerized with the application of phosphoramidite chemistry, biological properties of the different types of the bi- and tricyclic nucleotides containing oligomers were studied. Conformation of the molecules were determined by X-ray

diffraction, NMR measurments, and molecular dynamical calculations.

1.1.3. Morpholinos

At the end of the 20th century, a synthesis of a certain oligonucleotide derivative was reported, in which furanose moiety and phosphate ester backbone were also modified. Substituting the tetrahydrofuran of the ribofuranose with morpholine, these derivatives can be oligomerized with different bonds through the primary hydroxyl and the NH of the morpholine.

Various types of bonds were tested, and finally, the phosphorodiamidate bond was chosen, due to the costs and ease of synthesis and the chemical properties of the oligomers, e.g., target-binding, stability, watersolubility, and RNA-affinity. Oligomers produced with the above method are called phosphorodiamidate morpholino oligomers (PMOs).

Biological research has proven that PMOs are resistant against several degradating enzymes and seem to be promising therapeutic agents in the treatment of genetic disorders, e.g., Duchenne muscular distrophy, due to their binding efficacy and specificity as an antisense. Additionally, significant results were reported on their use in the treatment of certain infections, while in animal experiments, their activity worked effectively against dengue virus, Zaire Ebola virus, and influenzavirus, and inhibited the replication of the viruses.

1.1.4. Modified oligonucleotide derivatives in the therapy

The therapeutic application of modified oligonucleotide-based drugs has shown a remarkable development in the past twenty years. Fomivirsen was the first antisense used with AIDS patients in the treatment of CMV retinitis. Eteplirsen recevied accelerated approval from the FDA for the therapy of the aforementioned Duchenne muscular distrophy. Nusinersen was approved to treat another genetic disorder called spinal muscular atrophy. Mipomersen is used in the treatment of homozygous familiar hypercholesterolemia. Volanesorsen, currently in phase III clinical trials, seems to be a promising therapeutic agent, originally developed to treat hypertriglycidemia, familiar chylomicronemia syndrome and familiar partial lipodystrophy. A non-antisense, but oligonucleotide derivative, pegaptanib can be used in the therapy of Age-Related Macular Degeneration (AMD).

1.1.5. The reactions of tris(hydroxymethyl)aminomethane with different aldehydes and ketones

Previously, an *O,N*-acetal containing bicyclic derivative, 5-hydroxymethyl-3,7-dioxa-1-azabicyclo-[3.3.0]octane, was synthetized in the condensation reaction of 1:2 ratio of Tris and formaldehyde. In addition, the synthesis of a tricyclic derivative was also completed in the

reaction of Tris and hexane-2,5-dione in 1:1 ratio obtained 1,7-dimethyl-4-hydroxymethyl-2,6-dioxa-10-azatricyclo-[5.2.1.$0^{4,10}$]decane. A pentacyclic derivative, which was named „glytham", was synthetized with the stochiometric 2:2 ratio of cyclocondensation of glyoxal and Tris. The reaction took place with an excellent yield and full stereoselectivity. However, using other aminoalcohol derivatives (serinol és 2-amino-2-methyl-propane-1,3-diol), sidereactions were observed or the products were synthetized with low yields.

1.2. Aims of current PhD research

During my PhD research, the aim was to synthetize a novel type of nucleoside analogues from simple ribonucleosides. The secondary hydroxyls in 2' and 3' positions are oxidized by metaperiodate and the obtained secodialdehyde will be reacted with tris(hydroxymethyl)aminomethane (Tris) in a condensation reaction. With the three new stereogenic centers generated, potentially eight diastereomers can evolve in the produced novel tricyclic derivative.

For the synthesis, the application of the appropriate protecting groups and their removal after the tricyclization must be elaborated. The stereoselectivity of the reaction and the compatibility of the reagents and reactants with the protecting groups will be investigated, including investigating whether the stereoselectivity can be influenced by the applied protecting groups. In order to determine the structures of the intermediates and final products, mass spectrometry, NMR spectroscopy, conformational and DFT NMR calculation will be used. Additionally, X-ray crystallography will be needed for at least one derivative to determine the absolute configuration. Analysing the results can be generalized to define the structures of other compounds. Finally, unprotected derivatives can incorporate into nucleic acids, can cause chain ruption or can function as polymerase or other enzyme inhibitors. Therefore a collaborative investigation in the area of biological studies, such as cytotoxic and antiviral effects, is planned in the future.

2. Applied methods

Reactions were monitored by thin-layer chromatography. Crude products were purified by flash column chromatography. Optical rotations of the compounds were measured with polarimeter. MALDI-TOF and ESI-TOF mass spectrometry or ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC of 2D NMR methods were used for the structural determination of the compounds. In one case the absolute configuration of the compound was determined by X-ray crystallography, its data were used to define the structure of other derivatives with DFT NMR and conformational computational calculations.

3. New scientific results of the research

3.1. Developing a new method to remove triphenylmethyl-type protecting groups

In nucleoside chemistry trityl, mono- and dimethoxytrityl protecting groups are favored. These are usually cleaved by protic acids, e.g., HCl, HCOOH, AcOH, TsOH, F_3CCOOH, Cl_3CCOOH, $Cl_2CHCOOH$, and with the additional use of a reducing quenching agent Et_3SiH. In solid-phase oligonucleotide synthesis, the more acid-sensitive dimethoxytrityl is used, which can be removed by 2-3% of Cl_3CCOOH or $Cl_2CHCOOH$ in dichloromethane or toluene. However, the very harsh acidic conditions can cause depurination, especially in the case of 2'-deoxyadenosine.

However, the abovementioned reaction conditions are very robust for our tricyclic compound, so we had to develop a new method for the deprotection of triphenylmethyl type groups. Instead of protic acids, Lewis acids, such as $FeCl_3 \cdot H_2O$, $Yb(OTf)_3$, $Ce(OTf)_4$, $In(OTf)_3$, BCl_3, $ZnBr_2$, $BF_3 \cdot Et_2O$, $MgBr_2$ or TMSOTf/TESOTf can be used for the cleavage of trityl protecting groups. On the other hand, the mild protic acid 1,1,1,3,3,3-hexafluoroisopropanol can be an effective reagent in the removal of dimethoxytrityl. In addition, Et_3SiH can be also used as a reducing quenching agent along with Lewis acids. Some of these reagents are mild, but the reaction times are rather long in many cases, which may result in side reactions.

During this research, several experiments were carried out for the cleavage of the trityl protecting groups by some Lewis acids ($MgBr_2 \cdot Et_2O$, $Yb(OTf)_3$, $FeCl_3 \cdot H_2O$, $Cu(OTf)_2$, $BF_3 \cdot Et_2O$, $ZnCl_2$) with the combination of hexafluoroisopropanol and Et_3SiH. $Cu(OTf)_2$ and $BF_3 \cdot Et_2O$ proved to be the most promising, and reaction conditions were optimized on 5'-*O*-trityl-uridine as a model compound with the application of these two Lewis acids.

The mechanism of our three-component reagent combination can presumably be explained by the synergism of the components. Heteroatom is protonated by the mild protic acid hexafluoroisopropanol, similarly to the usual protic acids, as a result, triphenylmethyl-type cation and unprotected functional groups (OH, NH_2, SH) are formed. On the other hand, coordinating to the heteroatom, the Lewis acid can also cleave the protecting group, consequently, the generated triphenylmethyl-type cation is reduced by triethylsilane to a triphenylmethane derivative, shifting the equilibrium.

Following the optimization, the compatibility of our new reagent combination was studied with other protecting groups. A wide range of triphenylmethyl protecting groups was handled with the new reagent combination. *O*-Tr, *O*-DMTr, *N*-MMTr, *N*-Tr and *S*-Tr protecting groups of different types of carbohydrate, nucleoside and one cysteine derivatives were successfully removed in mild condition in a short period of time and in preparative scale.

Overall, the deprotections of the compounds resulted in good yields. Our new method is compatible with a wide range of protecting groups (*O*Ac, isopropylidene ketal, TBDMS ether, *N*-Bz or *N*-*i*PrCO and also *N*-Fmoc), and can be applied on various substrate. Moreover, depurination was never observed, which might cause problems in the standard detritylation of the solid-phase oligonucleotide synthesis.

3.2. Synthesis of tricyclic nucleoside analogues

After metaperiodate oxidation, the obtained secodialdehydes were reacted with tris(hydroxymethyl)aminomethane (Tris) and resulted in novel tricyclic nucleoside analogues. The produced anellated 3,7,10-trioxa-11-azatricyclo[5.3.1.$0^{5,11}$]undecane contains one morpholine and two oxazolidine rings which consist of a double *O*,*N*-acetal. Following the morpholino nucleosides, our new compounds were named tricyclanos. Previously different types of bridged and anellated bi-, tri- and pentacyclic heterocycles were synthetized in the condensation reaction between Tris and aldehydes or ketones, but the core heterocycle of the tricyclanos has not been published yet.

During the synthesis, three new stereogenic centres are generated, thus, potentially, eight diastereomers can evolve. However, only one main product was observed by thin layer chromatography in all cases. In some cases, the signs of a little unisolable side product are seen in the ^{1}H spectra by the chemical shifts of the H-1' and some CH or NH of the bases in 3-7%, presumably another diastereomer. Sometimes the tricyclano derivatives could be isolated with low or moderate yields, due to their poor solubility in organic solvents. It can be claimed that these reactions were carried out with high diastereoselectivity. The significance is that newly synthetized chiral active substances can be approved and marketed in enantio- or diastereopure form according to the latest guidelines.

3.2.1. Uracil-tricyclano

In the first step, uridine was transformed to the first tricyclano nucleoside analogue with a moderate yield for two steps, but with high diastereoselectivity. After that, the influence of the different protecting groups on the stereoselectivity and the yields were investigated. The TBDMS- and Tr-protected uracil-tricyclano derivatives were successfully synthetized with a significant increase of the yield. Finally, the TBDMS protecting group was removed with TBAF, and trityl ether was cleaved with our new reagent combination using $ZnCl_2$ instead of $BF_3{\cdot}Et_2O$ as Lewis acid. Additionally, the tritylated derivative was acetylated to produce a suitable sample for X-ray diffraction, but it was unavailable.

3.2.2. Hypoxanthine-tricyclano

As first attempt, the unprotected derivative was synthetized from inosine. Unfortunately, the product could be isolated with a low yield, most probably due to its low solubility. Next, tricyclization of the TBDMS- and Tr-derivatives were also carried out, following the proven method with the uridine derivatives, resulting in moderate yields. After that, deprotection procedures were completed, analogous with the uracil derivatives. The tritylated hypoxanthine-tricyclano was also acetylated. Finally, recrystallizing it from hot isopropanol, the absolute configuration of this derivative was successfully determined by X-ray crystallography.

3.2.3. Thymine-tricyclano

The tricyclization reaction of the ribothymidine derivative was also completed. Unprotected and tritylated ribothymidines were also transformed to their tricyclic derivatives. Removing the trityl group was also achieved, respectively. The unprotected thymine-tricyclano was acetylated to use in conformational and NMR computational calculation and to solve the structure determination.

3.2.4. Adenine-tricyclano

Given the low solubility of amino group containing nucleosides, it was by all means neccessary to use a protecting group. During the development of the protecting group strategy, triphenylmethyl types of protecting groups were chosen to protect the amino group. Consequently, *bis*trityl derivative of adenosine was synthetized with a good yield. After that, it was oxidized, and then the protected tricyclano derivative of adenosine was produced with a moderate yield. Unprotected adenine-tricyclano was obtained after removing the trityl groups with our new reagent system.

3.2.5. Cytosine-tricyclano

The tricyclic derivative of cytidine was synthetized from *bis*tritylated cytidine with a good yield. However, the cleavage of the trityl groups was only successful in the 5'-*O*-position. Accordingly, a decision was made to use the more acid label dimethoxytrityl. Starting with miscellaneous *N*-DMTr and *O*-Tr protected cytidine, the tricyclic derivative was synthetized with a good yield, which allowed for successfully producing the unprotected cytosine-tricyclano using our well-tried reagent combination. The low yield, in spite of the almost full conversion of the reaction, was most probably caused by the poor solubility of the product.

3.2.6. Guanine-tricyclano

At first, trityl protecting groups were also used for guanosine. The tricyclic derivative was produced with a good yield, but the expected compound could not be isolated after the detritylation. The double *O*,*N*-acetal was presumably hydrolized after a three-day reaction time. Reduction of the trityl groups with hydrogen and Pd/C catalyst or sodium naphtalenide was also tried, with no success.

Trusting the results with cytidine, *bis*(dimethoxytritylated) tricyclano derivative of guanosine was also synthetized, from which the unprotected guanine-tricyclano was isolated along moderate conversion of the reaction and with a very low yield. The partially deprotected derivative was also observed in the reaction mixture.

4. Summary

My PhD research focused on synthetizing a novel type of heterotricycle containing nucleoside analogues. The aim was to produce some biologically active compounds, given the fact that nucleoside or nucleotide analogue pharmacons are widely used in tumour and antiviral therapy. Additionally, there has been a remarkable development in applying oligonucleotide derivatives in the treatment and cure of rare, genetic, or metabolic diseases such as Duchenne muscular distrophy, spinal muscular atrophy, familiar hypercholesterolemia, hypertriglyceridemia, or age-related macular degeneration, etc.

The basic concept was inspired by the successful synthesis of different types of conformationally restricted bi- and tricyclic nucleoside derivatives, with some of them well researched in the various disciplines of biology. As a consequence of the restriction of carbohydrate moiety, these compounds became more resistant against degrading enzymes, hybridized with higher efficacy and specificity to natural nucleic acid chains, and induced the activation of RNase H.

Unprotected or suitably protected ribonucleosides were oxidized by metaperiodate to obtain secodialdehydes, which were reacted with Tris. In the condensation reaction, a new anellated heterotricyclic skeleton was formed. With the three new stereogenic centers of the tricycle, potentially eight diastereomers could evolve. However, the reactions were accomplished with high diastereoselectivity. Following the morpholinos, our new compounds were named tricyclanos.

To assign the structure of the tricyclanos, the absolute configuration of one of the tricyclano derivatives was successfully determined by X-ray diffraction. Next DFT NMR and conformationally calculations of three other compounds were compared with experimental NMR chemical shifts. Finally, as a result all four derivatives were homochiral.

During the synthesis, it was necessary to use suitable protecting groups, which are compatible with metaperiodate oxidation, tricyclization, and are easily removable. Considering these criteria, a new method was developed for the removal of triphenylmethyl-type protecting groups. Our new three-component reagent system contains a Lewis-acid, Et_3SiH, as a reducing quenching agent and hexafluoroisopropanol as mild protic acid. This reagent combination results in rapid and mild deprotection. Moreover, it is compatible with several protecting groups and is widely tunable. With the application of our novel method the tricyclano derivatives of uridine, inosine, ribothymidine, adenosine, cytidine, and even guanosine were successfully synthetized.

5. Scientific publications related to the dissertation

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Candidate: Máté Kicsák
Neptun ID: I00F0W
Doctoral School: Doctoral School of Pharmacy
MTMT ID: 10048006

List of publications related to the dissertation

1. **Kicsák, M.**, Mándi, A., Varga, S., Herczeg, M., Batta, G., Bényei, A., Borbás, A., Herczegh, P.: Tricyclanos: conformationally constrained nucleoside analogues with a new heterotricycle obtained from a D-ribofuranose unit.
   Org. Biomol. Chem. 16 (3), 393-401, 2018.
   DOI: http://dx.doi.org/10.1039/C7OB02296D
   IF: 3.564 (2016)
2. **Kicsák, M.**, Bege, M., Bereczki, I., Csávás, M., Herczeg, M., Kupihar, Z., Kovács, L., Borbás, A., Herczegh, P.: A three-component reagent system for rapid and mild removal of O-, N- and S-trityl protecting groups.
   Org. Biomol. Chem. 14 (12), 3190-3192, 2016.
   DOI: http://dx.doi.org/10.1039/C6OB00067C
   IF: 3.564

6. Other scientific publications

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List of other publications

3. Bege, M., Bereczki, I., Herczeg, M., **Kicsák, M.**, Eszenyi, D., Herczegh, P., Borbás, A.: A low-temperature, photoinduced thiol-ene click reaction: a mild and efficient method for the synthesis of sugar-modified nucleosides.
Org. Biomol. Chem. 15 (43), 9226-9233, 2017.
DOI: http://dx.doi.org/10.1039/C7OB02184D
IF: 3.564 (2016)

4. Bereczki, I., **Kicsák, M.**, Dobray, L., Borbás, A., Batta, G., Kéki, S., Nemes Nikodém, É., Ostorházi, E., Rozgonyi, F., Vanderlinden, E., Naesens, L., Herczegh, P.: Semisynthetic teicoplanin derivatives as new influenza virus binding inhibitors: synthesis and antiviral studies.
Bioorg. Med. Chem. Lett. 24 (15), 3251-3254, 2014.
DOI: http://dx.doi.org/10.1016/j.bmcl.2014.06.018
IF: 2.42

Total IF of journals (all publications): 13,112
Total IF of journals (publications related to the dissertation): 7,128

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

07 March, 2018

DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *

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