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Pharmacokinetic profiling of some carbohydrate derivatives and their structure activity relationship evaluation

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Running Head: TLC application in estimation of lipophilicity

Abstract

Background: Carbohydrates are of great interest for the synthesis of novel ribonucleosides and *C*-Nucleosides which often show different pharmacological potential including antiinflammatory and antineoplastic characteristics. In this research twelve aldopentose derivatives are examined and their chromatographic properties are used to describe their pharmacokinetic profiles.

Methods: Thin layer chromatography was performed using three mobile phases: acetone–water (ϕ = 0.5–0.7 v/v), dioxane–water (ϕ = 0.5—0.7 v/v) and methanol–water (ϕ = 0.5–0.7 v/v). Multiple linear regression was performed in order to obtain pharmacokinetic properties of the examined molecules.

Results: Good oral absorption can be expected for all investigated compounds. Moderate volume of distribution indicates low to moderate probability of their accumulation in body tissues. All investigated molecules show good pharmacokinetic characteristics but compounds 2, 3, 5, 6 and 7 demonstrated the best biological potential and biochemical activity such as inhibition of protease and kinase (compound 7) and possibility to be a ligand for GPCR.

Conclusion: Among the best candidates authors would emphasize structure 7 as the most promised molecule regarding its pharmacological potential.

Keywords: aldopentose, multiple linear regression, QSAR, pharmacokinetic, ADME

Introduction

Carbohydrate derivatives represent important compounds used as building blocks in organic synthesis of various biomolecules. They are often used not only as intermediates, but also as starting molecules in the different synthetic processes. As a specific subgroup of carbohydrate compounds, aldopentose derivatives represent promising starting material for various syntheses of ribonucleosides as well as certain C-nucleosides with potential antitumor and/or antiviral properties. Usually they are produced using corncobs or a similar natural waste material containing large amounts of xylan or hemicellulose which makes them cheap source in production of bioactive molecules (1). Because of chiral characteristics their stereochemical and conformational properties are exploited in the field of synthetic chemistry. A number of twelve derivatives of aldopentoses that are discussed in this research have been used in the synthesis of different *C*-nucleosides. It has been discovered that few *C*-nucleosides show certain pharmacological potential e.g. pseudouridine and showdomycin. Aldopentose derivatives represent stabile intermediates while natural and synthetic *N*-nucleosides are sensitive to enzymatic and acid hydrolysis. There is a number of various applications of *C*-nucleosides in medicinal chemistry discovering antiviral, antibacterial and antitumor properties (2). However in order to unlock their full biological potential some other examinations of their pharmacokinetic and pharmacodynamics properties are necessary.

One of the important factors that dictate behavior of a specific compound is lipophilicity. Lipophilicity is directly connected to the ability of the compound to interfere with biological barriers and thus represents a credible parameter that can be used to describe pharmacokinetic, pharmacodynamics and toxic features of investigated compounds (3). By overcoming traditional ''shake flask'' method and using liquid chromatography for consequently calculation of lipophilicity, a revolution was brought to the modern QSAR studies. Liquid chromatography has been widely accepted and proved to be more accurate and less complicated than traditional methods. Basic principle of this method is to apply calculated retention values for building relations with significant molecular descriptors (4).

In silico tools are of great importance in modern research. The simplicity of using measured physicochemical parameters and their successively analyse using different computer software brought incredible ammount of useful data in scientific world. Modern QSAR studies are widely used as a first filter that can eliminate compounds that do not meet the criteria essential for extensive clinical or industrial usage. Knowledge gained through adequate QSAR studies can eliminate unnecessarily time and funding spent on clinical researches and can lead to optimised processes in which only the most suitable candidates are used. Therefore the aim of this method is to develop a model that would be able to describe specific behaviour of examined aldopentose derivatives with the best statistical significance.

Structures of the twelve compounds that are examined in this paper are presented in Figure 1.

The goal of the work discussed in this paper was to investigate the correlation between the retention constants such as lipophilicity of aldopentose derivatives and selected pharmacokinetic and pharmacodynamic descriptors in order to develop model that can be utilized to determine which of the investigated compounds should be further examinated in biological tests and could potentially be used as building block in synthesis of new *C*-Nucleosides and ribonucleosides.

Materials and methods

Investigated aldopentose derivatives were previously synthetized according to the procedure of Popsavin et al. (5). Thin layer chromatography was performed on 20x20cm silica gel impregnate glass plates at University of Novi Sad using the mobile phases: acetone–water (ϕ = 0.5–0.7 v/v), dioxane–water (ϕ = 0.5—0.7 v/v) and methanol–water (ϕ = 0.5–0.7 v/v) (6). Previously calculated retention constants of aldopentose derivatives were used in different calculations in order to obtain correlation between these constants and pharmacokinetic parameters such as: HIA, DBP, *V*d and SP. GPCR, KI and PI values were calculated using Molinspiration software and evaluated using multiple linear regression analysis. Several software programs were used (https://ilab.acdlabs.com/iLab2/ , www.molinspiration.com , http://preadmet.bmdrc.kr/) in obtaining different parameters. Calculations and graphics presented in this paper were done using OriginPro 2016 software package.

Results

Chromatography is driven by different intermolecular interactions between the solvent, analyzed components and solid surface. These interactions are enabled due to various parameters, but one of the most important is polarity. By adjusting the polarity of a solvent, the separation of compounds can be performed with better resolution and effectiveness. Results gained from chromatography can be used in describing lipophilicity of examined compounds, but also contribute as starting parameters for further QSAR calculations (3). In order to achieve this it is necessary to prove that chromatographic parameters can accurately represent lipophilicity of investigated compounds.

Previously reported results presented different logP values were gained and correlated through the use of several software programs. Good predictive ability of selected parameters was proved and dependence between chromatographic parameters and different descriptors of lipophilicity was obtained (7).

The retention constants (R_M) values were calculated according to following equation:

$R_M=\log(1/R_f-1)$ (1)

Where R_f is retention factor. R_M values linearly depend on the logarithm of concentration of the organic modifier in the mobile phase toward to the relation:

$R_M=R_M^0+b\log C$ (2)

Linear dependence from R_M^0 (intercept) to b (slope) for three solvent systems is obtained by following functions:

$R_M^0{}_1=-0,9103b_1-1,1625$ ($r^2=0,9480$) (3)

$R_M^0{}_2=-0,879b_2-1,0977$ ($r^2=0,9824$) (4)

$R_M^0{}_3=-0,6263b_3-0,0343$ ($r^2=0,8471$) (5)

$C_{01}= -0,1515R_M^0{}_1+0,2471$ ($r^2=0,9120$) (6)

$C_{02}= 0,1494R_M^0{}_2+0,2574$ ($r^2=0,9435$) (7)

$C_{03}= 0,1091R_M^0{}_3+0,2036$ ($r^2=0,8467$) (8)

which confirms that this group of molecules behaves like congeneric group. Correlations in equations 3 and 4 are presented graphically and are shown in Figures 3 and 4 . After a congeneric group behavior of investigated substances was proved it became possible to calculate further pharmacokinetic and pharmacodynamics parameters that are important for QSAR studies.

Relevant data concerning the prediction of intestinal absorption and tissue distribution is required in order to achieve potentially more rational drug administration. Although investigated molecules contain a large number of groups that can undergo acidic hydrolysis in stomach this effect can be avoid using modern drug formulations such as chitosan coated liposomes. According to the known Lipinski's ''rule of 5'', poor absorption or permeation are more expected when: there are more than 5 H-bond donors (expressed as the sum of

nitrogens and oxygens); the molecular weight is over 500; the log*P* is over 5 (or MlogP is over 4,15); there are more than 10 H-bond acceptors (expressed as the sum of N and O atoms) (8). These parameters are presented in Table 1.

In order to gain a more detailed pharmacokinetic profile of investigated aldopentose derivatives additional molecular descriptors were introduced and estimated using different software programs (http://www.molinspiration.com/, https://ilab.acdlabs.com/iLab2/, http://preadmet.bmdrc.kr/description-of-preadmet/). These descriptors are logKa– logarithm of dissociation constant; HIA- human intestinal absorption in percent; DBP- plasma protein bound in percent; *V*d- human volume of distribution (l/kg) and SP- skin permeability. All of this factors are important for several stages of compound`s passage through different biological barriers (Table 2).

Modern QSAR studies suggest calculating various bioactivity parameters in order to beforehand comprehend possible biological effects that are caused by binding with different proteins in human body (9). Bioactivity scores were calculated using Molinspiration software. These parameters are G-Protein coupled receptors ligand (GPCR), kinase inhibition (KI), protease inhibition (PI) and they are shown in Table 3. Calculated values can indicate binding affinity of investigated aldopentose derivatives to the mentioned receptors and enzymes. In order to accurately interpret these results is it necessary to know that negative values represent low affinity, while positive values indicate high affinity.

Modern QSAR studies suggest calculating probability for antineoplastic and anti-inflammatory activity as a sign of possible additional valuable effects in humans (10). These parameters were calculated using Way2Drug software and are presented in Table 4.

Discussion

Using Molinspiration software physicochemical parameters that are of importance for Lipinski's ''rule of 5'' were calculated and results are shown in Table 1. It can be noticed that some of the compounds such as 3, 5, 6, 11 and 12 violate only one rule because their relative molecule weight exceed 500. However, according to Lipinski, in case of only one violation a good oral absorption can still be expected (8). Total polar surface area (TPSA), number of rotatable bonds (nrotb) and molecular volume (V) are not usually included in Lipinski's ''rule of 5'', but are also important for a better understanding of oral bioavailability of examined compounds. When a certain substance obeys these rules a good oral bioavailability is possible and it is additional proof of a good pharmacokinetic behavior.

The equilibrium constant of an acid is represented by pKa value which indicates the ratio of the dissociated and undissociated components (11). Hence logpKa values are used to estimate acidic or basic properties of investigated compounds. The range of calculated

logpKa values for investigated compounds varies from 2,90 to 4,61. Modern QSAR studies suggest that combining different factors that are directly connected to the lipophilicity is of better statistical quality when compared to the models that are only based on chromatographic parameters (12). After introducing additional descriptors, which were total polar surface area (TPSA) and molecular weight (Mw), multiple linear regression analysis was performed for logpKa and the models with best statistical parameters are represented in the following equations:

$$\text{logpKa}=0{,}493R_M{}^0{}_1+1{,}04\text{x}10^{-3}\text{TPSA}+1{,}71\text{x}10^{-3}\text{Mw}+2{,}137 \quad (r^2=0{,}794,\ F=15{,}146,\ p=1{,}16\text{x}10^{-3}) \qquad (9)$$

$$\text{logpKa}=0{,}770R_M{}^0{}_2-1{,}71\text{x}10^{-3}\text{TPSA}+3{,}42\text{x}10^{-3}\text{Mw}+1{,}201 \ (r^2=0{,}74,\ F=10{,}458,\ p=5{,}59\text{x}10^{-3}) \qquad (10)$$

$$\text{logpKa}=0{,}295R_M{}^0{}_3-1{,}25\text{x}10^{-3}\text{TPSA}+1{,}29\text{x}10^{3}\text{Mw}+2{,}491 \ (r^2=0{,}87,\ F=21{,}14,\ p=1{,}37\text{x}10^{-3}) \qquad (11)$$

The jejunum represents a part of digestive system where most of the drugs are absorbed. The prediction of jejunum absorption represents an unavoidable part of modern QSAR studies (13). Using ACD-i-lab and PREADMET software packages two important parameters (HIA and $Pe_{(jejunum)}$) were calculated and they are useful for further investigation of compound's destiny in intestines. Results for these parameters can be seen in Table 2. All examined molecules possess HIA values higher than 80% which suggests that well intestinal absorption is to be assumed. Regarding to the other parameters which affects absorption process, modern QSPR offers approach which includes introducing of different factors that could lead to better predictive quality of the established mathematical model. Additional descriptors e.g. total polar surface area (TPSA) and molecular weight (M_w) were considered in this work and were added into multiple linear regression analysis calculations. Gained models for HIA and $Pe_{(jejunum)}$ can be used to predict the behavior of investigated compound in intestine with a high statistical significance and their ability to be delivered to blood system. Tridimensional models for $Pe_{(jejunum)}$ are shown in Figure 4.

$$\text{HIA}=5{,}226R_M{}^0{}_1-0{,}056\text{TPSA}+0{,}016M_w+82{,}628 \ (r^2=0{,}827,\ F=18{,}523,\ p=5{,}853\text{x}10^{-4}) \qquad (12)$$

$$\text{HIA}=-4{,}593S_1-0{,}021\text{TPSA}+0{,}017M_w+73{,}144 \ (r^2=0{,}750,\ F=11{,}990,\ p=2{,}49\text{x}10^{-3}) \qquad (13)$$

$$\text{HIA}=2{,}977R_M{}^0{}_3-0{,}091\text{TPSA}+0{,}011M_w+87{,}806 \ (r^2=0{,}853,\ F=18{,}450,\ p=1{,}97\text{x}10^{-3}) \qquad (14)$$

$$\text{HIA}=-2{,}108S_3-0{,}127\text{TPSA}+5{,}99\text{x}10^{-3}M_w+92{,}079 \ (r^2=0{,}78,\ F=11{,}649,\ p=6{,}49\text{x}10^{-3}) \qquad (15)$$

$$Pe_{(jejunum)}=2{,}168\text{x}10^{-4}R_M{}^0{}_1-1{,}4154\text{x}10^{-6}\text{TPSA}-6{,}586\text{x}10^{-8}\text{Mw}+3{,}472\text{x}10^{-4} \ (r^2=0{,}863,\ F=24{,}103,\ p=2{,}324\text{x}10^{-4}) \qquad (16)$$

$$Pe_{(jejunum)}=1{,}286\text{x}10^{-4}R_M{}^0{}_2+4{,}984\text{x}10^{-7}\text{TPSA}-7{,}637\text{x}10^{-7}\text{Mw}+7{,}345\text{x}10^{-4} \ (r^2=0{,}714,\ F=9{,}342,\ p=7{,}63\text{x}10^{-3}) \qquad (17)$$

$Pe_{(jejunum)}$=1,236x10^{-4}$R_M{}^0{}_3$-2,505x10^{-6}TPSA-2,316x10^{-7}Mw+5,224x10^{-4} (r^2=0,861, F=19,535, p=1,69x10^{-3}) (18)

A next partitioning step in transport of the substance through human body is its distribution. From various units used to describe distribution volume of distribution (*V*d) dominates in the field of QSAR studies. Volume of distribution has no direct physical or anatomical meaning, but it represents a measure of relative partitioning of a drug between plasma and the tissues (14). *V*d is directly correlated with the amount of drug distributed into tissue; a higher *V*d indicates a greater amount of tissue distribution and otherwise. Using PreADMET software values for *V*d of the investigated compounds were calculated and they can be seen in Table 2. Knowing that all of the examined compounds behave as weak acids due to their chemical nature, it was to be expected that predicted values will be moderate and that peripheral accumulation is not to be foreseen.

Using the same approach as for the other parameters, after adding additional molecular descriptors (TPSA and M_w) and by using multiple linear analyze models with satisfying correlation coefficients were obtained and are shown in the equations 19, 20 and 21. It is also to be observed that the statistical parameters for the third solution system are the most significant.

*V*d=0,493$R_M{}^0{}_1$+1,04x10^{-3}TPSA+1,71x10^{-3}M_w+2,137 (r^2=0,794, F=15,146, p=1,16x10^{-3}) (19)

*V*d=0,77$R_M{}^0{}_2$-1,71x10^{-3}TPSA+3,42x10^{-3}M_w+1,201 (r^2=0,74, F=10,458, p=5,59x10^{-3}) (20)

*V*d=0,296$R_M{}^0{}_3$-1,25x10^{-3}TPSA+1,29x10^{-3}M_w+2,491 (r^2=0,87, F=21,14, p=1,37x10^{-3}) (21)

PreADMET software is also able to calculate skin permeability value. In order to gain complete profile of all possible ways of application of a certain compounds, skin permeability (SP) represents an important factor. Skin permeability dictates the possibility of transdermal delivery, which in certain cases can be the most beneficial one. The results obtained with this software are given as logKp.

Kp (cm/h) is defined as:

$Kp = (Km \cdot D)/h$

where Km is distribution coefficient between stratum corneum and vehicle, D is average diffusion coefficient (cm^2/h) and h is thickness of skin (cm).

From the results gained in this study a good skin penetration is not to be expected, which is in accordance to their carboxyhydratic nature. However, compounds 11 and 12 show tendency for a higher degree of skin penetration because of their slightly more polar nature when compared to other candidates. Using OriginPro 2016 software models that explain this

behavior were developed and their statistical significance was improved when two additional parameters (TPSA and M_w) were added.

$SP=-0,32{R_M}^0{}_1+0,013TPSA+2,4x10^{-3}M_w-7,011$ ($r^2=0,955$, $F=79,945$, $p=2,637x10^{-6}$) (22)

$SP=0,959{R_M}^0{}_2+0,0126TPSA+3,3x10^{-3}M_w-7,474$ ($r^2=0,866$, $F=22,554$, $p=5,656x10^{-4}$) (23)

$SP=0,454\ {R_M}^0{}_3+8,68x10^{-3}TPSA+1,92x10^{-3}M_w-6,392$ ($r^2=0,962$, $F=77,775$, $p=3,414x10^{-5}$) (24)

After a successful absorption through different barriers, an important characteristic of various xenobiotics is the ability to bind with proteins in red blood cells. This partitioning process is a vital key in determination of the size unbound fraction, which is the only fraction that can pass biological barriers and consequentially manifest a certain effect. On the other side, bound fraction represents an important depot from which a drug can be released in the certain amount of time (13, 14). Having in mind all of these facts, binding with plasma proteins is important factor not only for pharmacokinetic but also for a pharmacodynamics of a certain compound. Candidates that bind themselves with blood proteins in higher percent are desirable in QSAR studies. Therefore, a molecule descriptor called ''DBP- plasma protein bound in percent'' was introduced in calculations.

Investigated aldopentose have satisfactory DBP values shown in Table 2. Since most of the compounds are predicted to bind to plasma proteins with a fraction bigger than 90% controlled release is to be expected. Fractions of compound 6 and 7 will be significantly lower bonded to the proteins in red blood cells and general opinion is that less lipophilic compounds are predicted to bind less to these carriers. DBP was further tested as a function depending of retention constants important for the binding possibility - TPSA and M_w. After multiple linear regression analysis was performed it was possible to obtain models that are useful for describing of the affinity for binding to plasma proteins (Equations 25-27). Visual representation of calculated model for acetone-water system can be seen in Figure 5.

$DBP=23,596{R_M}^0{}_1-0,0522TPSA+0,044M_w+21,598$ ($r^2=0,9136$, $F=39,773$, $p=3,738x10^{-5}$) (25)

$DBP=23,597{R_M}^0{}_2-0,0522TPSA+0,0438M_w+21,598$ ($r^2=0,914$, $F=39,773$, $p=3,738x10^{-5}$) (26)

$DBP=13,589\ {R_M}^0{}_3-0,176TPSA+0,025M_w+40,975$ ($r^2=0,943$, $F=50,497$, $p=1,192x10^{-4}$) (27)

G protein-coupled receptors (GPCRs) play important role in wide variety of physiological process in humans. These membrane proteins are responsible for human growth, reproduction, immune cell migration, nerve conduction, metabolism and behavior and are related to human diseases such as tumors, inflammation, obesity, diabetes, osteoporosis (15, 16). Therefore, for modern QSAR discovering of novel substances GPCRs ligands represent major achievement. Using Molinspiration software affinity of investigated compounds for GPCRs was examined. Binding to GPCRs is multilayered action since the the accurate size of GPCR superfamily is not completely defined and polymorphism is much accented (17). Compound 7 shows the largest potential for binding to GPCR and this could

be explained by the presence of two hydroxyl groups in the chemical structure. In according to correlation between lipophilicity and bioactivity scores it was possible to calculate molecular models using OriginPro 2016 and they are presented in following equations.

$$GPCR=-0,117\ {}^{0}R_{M1}+0,002TPSA-4,978x10^{-4}M_w+0,405\ (r^2=0,635,\ F=7,381,\ p=1,083x10^{-2}) \quad (28)$$

$$GPCR=0,109S_1+0,0012TPSA-5,151x10^{-4}M_w+0,636\ (r^2=0,675,\ F=8,63,\ p=6,88x10^{-3}) \quad (29)$$

Kinase enzymes have been involved in several steps of tumor progression including proliferation, motility, metabolism, angiogenesis and evasion of antitumor immune responses. Thus kinase inhibitory potential plays an important role in the discovering of new compounds with antitumor activity (18). After calculating appropriate bioactivity scores it was concluded that among the investigated molecules compound 7 shows weakest potential to inhibit kinase.

$$KI=-0,101\ {}^{0}R_{M1}+0,0022TPSA+1,888x10^{-4}M_w-0,193\ (r^2=0,803,\ F=13,241,\ p=4,69x10^{-3}) \quad (30)$$

$$KI=0,0862S_1+1,64x10^{-3}TPSA+9,278x10^{-5}M_w+6,14x10^{-3}\ (r^2=0,777,\ F=11,492,\ p=6,72x10^{-3}) \quad (31)$$

$$KI=-0,0614\ {}^{0}R_{M3}+2,28x10^{-3}TPSA+3,177x10^{-4}M_w-0,239\ (r^2=0,775,\ F=9,060,\ p=0,0295) \quad (32)$$

$$KI=0,0447S_3+0,00304TPSA+4,492x10^{-4}M_w-0,3322\ (r^2=0,712,\ F=6,782,\ p=0,0477) \quad (33)$$

Protease inhibitory activity is characteristic for medicines that are used in the treatment of HIV infections. *C*-Nucleosides found applications in design of new compounds that possess anti HIV potential (19). Affinity for the inhibition of this important enzyme was between -0,04 and 0,27. Gathered information gives the conclusion that the best inhibitory activity was showed by structures 7 and 8.

$$PI=-0,043\ {}^{0}R_{M3}+2,46x10^{-3}TPSA-2,355M_w+0,126\ (r^2=0,676,\ F=7,277,\ p=0,02) \quad (35)$$

$$PI=0,0333S_3+0,003TPSA-1,346x10^{-4}M_w+0,0588\ (r^2=0,756,\ F=10,311,\ p=8,79x10^{-3}) \quad (36)$$

Antitumor and anti-inflammatory activity of novel compounds represents the focus of interest in modern research. Using Way2Drug (http://www.way2drug.com/) software values for investigated aldopentose were calculated and they are shown in Table 4. Probability higher than 0,6 indicates that a significant effect on tumor growth or inflammatory process is expected and candidates who possess mentioned scores can be future investigated in order to clarify their potential beneficial effect. For compounds 5, 6 and 7 the biggest affinity to play an important role in these processes is predicted.

Conclusion

In this research twelwe aldopentose derivatives were studied. Their lipophilicity was determined using reversed phase thin layer chromatography under three different mobile

phases conditions. As a predictive analysis, the multiple linear regression is used to explain the relationship between dependent pharmacokinetic variables from independent variables R_M^0, *b*, TPSA and/or M_w. Lipophilicity is the most promised physicochemical parameter used in determination of humane intestinal absorption and passage through phospholipid bilayer in jejunum. Good oral absorption can be expected for all investigated compounds. Moderate volume of distribution indicates low to moderate probability of their accumulation in body tissues. This conclusion can be supported with good affinity for binding with plasma proteins which lowers the chance for toxicity. Penetration level through blood-brain barrier and skin is not satisfactory which is beneficial because it can lead to lower possibility of adverse effects. Compound 7 has a good affinity for binding with G-protein coupled receptors, while compounds 2, 3, 4 and 5 possess lower ability. Compound 2 and 3 show lower antiimflamatory and antineoplastic potential than compounds 5, 6 and 7. Regarding to good pharmacokinetic profile of the investigated molecules authors would propose compounds 2, 3, 5, 6 and 7 as most suitable candidates for future investigation.

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Conflict of interest

The authors have declare no conflict of interest to dislocure.

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