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RESEARCH ARTICLE

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α-Glucosidase inhibitory activity and cytotoxic effects of some cyclic urea and carbamate derivatives

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ABSTRACT

The inhibitory activities of selected cyclic urea and carbamate derivatives (**1**–**13**) toward α-glucosidase (α-Gls) in *in vitro* assay were examined in this study. All examined compounds showed higher inhibitory activity (IC_{50}) against α-Gls compared to standard antidiabetic drug acarbose. The most potent was benzyl (3,4,5-trimethoxyphenyl)carbamate (**12**) with $IC_{50} = 49.85 \pm 0.10$ μM. *In vitro* cytotoxicity of the investigated compounds was tested on three human cancer cell lines HeLa, A549 and MDA-MB-453 using MTT assay. The best antitumour activity was achieved with compound **2** (*trans*-5-phenethyl-1-phenylhexahydro-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-one) against MDA-MB-453 human breast cancer cell line ($IC_{50} = 83.41 \pm 1.60$ μM). Cyclic ureas and carbamates showed promising anti-α-glucosidase activity and should be further tested as potential antidiabetic drugs. The PLS model of preliminary QSAR study indicated that, in planing the future synthesis of more potent compounds, the newly designed should have the substituents capable of polar interactions with receptor sites in various positions, while avoiding the increase of their lipophilicity.

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KEYWORDS
α-Glucosidase inhibitors; carbamates; cyclic ureas; cytotoxicity; QSAR

Introduction

Diabetes mellitus type 2 (DMT2) is an endocrine disease of global proportions which is currently affecting 1 out of 12 adults in the world, with still increasing prevalence[1]. World Health Organization (WHO) declared this worldwide health problem as an epidemic disease to be the only noninfectious disease with such categorization[2]. This deadly disease is associated with numerous side effects such as impairment of functions of kidneys, heart, eye and nervous system affecting carbohydrate, protein and fat metabolism[3]. The main classes of oral antidiabetic drugs accessible today for DMT2 vary in their chemical composition, modes of action, safety profiles and tolerability[4]. Both the insulin resistance and the decrease in insulin production over time, allow the treatment of people suffering from DMT2 with a wide range of drugs that are available on the market[5]. Insulin, sulfonylureas, the metiglinides, insulin sensitizers, biguanides and α-glucosidase inhibitors belong to the group of traditional antidiabetics developed during the twentieth century[2,6] while the newer drugs such as GLP-1 analogs, DPP-VI inhibitors, amylin analogs and SGLT2 inhibitors emerged during the past decade[2,7].

α-Glucosidase (α-Gls) inhibitors postpone digestion and absorption of intestinal carbohydrate[3,4]. They are agents convenient for the reduction of postprandial hyperglycemia by suppressing the absorption of glucose, hence being effective in the treatment of T2 diabetes and obesity. Besides, the current interest in α-Gls inhibitors has been extended to a broad range of diseases including lysosomal storage disorders and cancer, and HIV infection[8,9]. Amongst the various types of α-Gls inhibitors, disaccharides, iminosugars, carbasugars, thiosugars, and non-sugar derivatives have received great attention[9]. Since 1990s, acarbose (Glucobay®, Precose®, Prandase®), voglibose (Basen®), and miglitol (Glyset®) (Figure 1) have been used for the treatment of diabetes[10]. However, complicated multi-step synthetic procedures imposed a need for the synthesis of compounds with no structural similarity to the above compounds. Such compounds represent a new class of inhibitors that are of major interest. The elucidation of their mechanism of action may add new insights in the search for new therapeutic agents[9]. Most recently, benzimidazole derivatives, dihydropyrano[2,3-*c*]pyrazoles have been evaluated as α-Gls inhibitors[11–13]. A series of indoline carbamate and indolinylpyrimidine derivatives have been discovered as potent GPR119 agonists, and are expected to serve as novel anti-diabetic agents[14].

Due to the importance of antidiabetic agents and their role in controlling diabetes-related mortality, the search for newer antidiabetic drugs continues. Among the others, heterocyclic molecules with antidiabetic activity have a place in the most perspective fields of the research[2].

Previous work in our laboratory resulted in the development of the one-pot procedure for the Hofmann rearrangement of aromatic or aliphatic amides, which led to the synthesis of a series of carbamates and cyclic ureas[15]. With regard to the synthesis of these classes of compounds, different protocols have been reported in the literature[16,17]. Carbamate derivatives with a recognizable –O–CO–NH– moiety encompass multiple applications in bioorganic and medicinal chemistry[18–24]. Cyclic ureas are synthetically useful intermediates, particularly as precursors to

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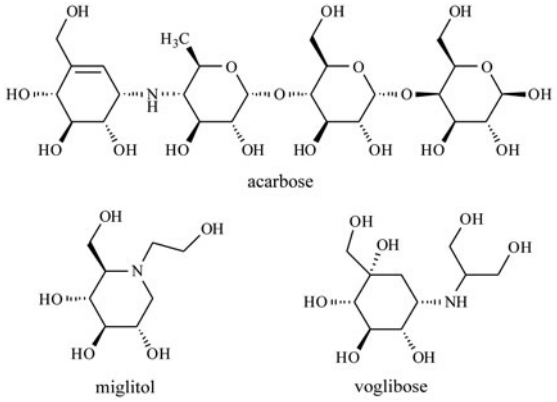

Figure 1. α-Gls inhibitors used as antidiabetic drugs.

pharmacologically active imidazoles[15]. Moreover, in the 1990s these compounds have been a part of intensive researches on the human immunodeficiency virus (HIV – the causative agent of AIDS), which revealed that certain derivatives of cyclic ureas act as potent HIV protease inhibitors[25,26].

The results of the selected cyclic urea and carbamate derivatives for the inhibitory activity against α-Gls are being reported herein. In addition, *in vitro* cytotoxicity of the examined compounds was tested toward three human cancer cell lines: cervix adenocarcinoma (HeLa), non-small cell lung carcinoma (A549) and human breast cancer (MDA-MB-453). QSAR analysis was attempted on activity against α-glucosidase by applying PLS (Partial Least Square) regression analysis. The interpretation of descriptors which are included in PLS model can help us in better understanding and explanation of biological behaviour of investigated compounds.

Materials and methods

Chemistry

Unless stated otherwise, all the commercially available reagents and solvents were used as supplied. α-Gls from *Saccharomyces cerevisiae*, RPMI 1640 (product number R8755), *p*-nitrophenyl α-D-glucopyranoside (PNP-G), acarbose, fetal bovine serum (FCS), dimethyl sulfoxide (DMSO), hepes, ethidium bromide, sodium dodecyl sulfate (SDS), acridine orange, disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate and thiazolyl blue tetrazolium bromide (MTT) were purchased from Sigma-Aldrich (St. Louis, MO). Trypsin and phosphate buffered saline (PBS) were obtained from Institute of Virology, Vaccines and Sera "Torlak", Belgrade, Serbia.

General procedure for the preparation of cyclic ureas and carbamates

Cyclic urea (**1**–**5**) and carbamate derivatives (**6**–**13**) were synthesized by a novel procedure described in our previous paper[15].

Anti α-glucosidase activity

Anti-α-Gls activity of compounds was determined using an α-Gls inhibitory activity test described by McCue et al. with some modification[27]. The enzyme solution was set at 400 mU/mL of α-Gls in a 0.1M phosphate buffer (pH = 6.8). For each well we used 50 µL of the tested compounds in DMSO, diluted in a 0.1M phosphate buffer (pH = 6.8). The final concentrations of the extracts in each well were 166.67, 83.33, 41.67, 20.83, 10.42, 5.21 µM. In 96-well plates, 50 µL of extract dilutions was preincubated with 50 µL of enzyme solution for each well at 37 °C for 15 min. The reaction was started by adding 50 µL of substrate solution, *p*-nitrophenyl α-D-glucopyranoside (1.5 mg/mL PNP-G in phosphate buffer) and after measuring absorbance A1 at 405 nm the solution was incubated at 37 °C for 15 min. Second absorbance A2 was measured at 405 nm. Acarbose was used as a positive control. The percent of the enzyme inhibition was calculated as $100 \times (A2S–A1S)/(A2B–A1B)$, A1B, A2B and A1S, A2S representing the absorbance of the blank (phosphate buffer, DMSO, enzyme dilution, and PNP–G dilution) and sample, respectively. The experiments were conducted in duplicate and IC_{50} value (estimated concentration of compounds that caused 50% inhibition of α-Gls activity) was determined using linear regression analysis.

MTT assay

Cytotoxic activity

Incubation of the cultures was performed according to the literature procedure[28]. Target cells HeLa, cervix adenocarcinoma cell line (2000 cells per well), A549, non-small cell lung carcinoma cell line (5000 cells per well) and MDA-MB-453 human breast cancer cell line (3000 cells per well) were seeded into 96-well plate. Twenty-four hours later different concentrations of investigated compounds were added to the wells, except for the control cells to which a nutrient medium was added. The final concentrations range was 1–200 µM (12.50, 25, 50, 100, and 200 µM). The final concentration of DMSO solvent never exceeded 0.5%, which was non-toxic to the cells. All concentrations were set up in triplicate. Nutrient medium with corresponding concentrations of investigated compounds, but without cells, was used as a blank, also in triplicate. The cultures were incubated for 72 h.

Determination of cell survival The effect of the investigated compounds on cancer cell survival was determined by the microculture tetrazolium test (MTT) according to Mosmann[29] with modification by Ohno and Abe[30], 72 h after the addition of the compounds, as previously described[28]. All experiments were done in triplicate.

Morphological evaluation of cell death After 24 h of seeding 80 000 HeLa cells per well, they were treated with compound dilutions of IC_{50} and $2 \times IC_{50}$ in control only nutrient medium was added. After another 24 h of incubation cells were stained with acridine orange AO and ethidium bromide EB (3 µg/mLAO +10 µg/mL EB in PBS), then visualized under a fluorescence microscope (Carl Zeiss, Oberkochen, Germany) PALM MicroBeam with Axio Observer.Z1 using AxioCam MRm (filters Alexa 488 and 568), as described in literature[31].

Calculation of molecular descriptors

All structures were built using the Maestro 10.1 from Schrödinger Suite 2015-1 (Maestro, version 10.1, Schrödinger, LLC, New York, NY). QikProp version 4.3 (QikProp, version 4.3, Schrödinger, LLC, New York, NY) was used for the calculation of physically significant molecular descriptors and pharmaceutically relevant properties. Single-point calculations using the RM1 method[32] from Semiempirical NDDO module of Scrodinger Suite 2015-1 was used for semiempirical parameters. The calculated molecular descriptors

which are used in final PLS regression analysis are given in Table S1 (Supplemental Information).

Multivariate statistical analysis and modelling

PLS has been performed using a demo version of PLS_Toolbox statistical package (Eigenvectors, v. 5.7) for MATLAB version 7.4.0.287 (R2007a) (MathWorks, Natick, MA). The data were autoscaled before building the model in order to prevent variables with larger magnitude to prevail in the final model. The PLS method calculates latent variables for both independent and dependent variable matrices plus a relationship between them. Validation of the models was performed using the leave-one-out cross-validation procedure.

The quality of the regression fits was monitored with the R^2_{cal}, (cumulative sum of squares of the *Ys* explained by all extracted components) and R^2_{CV} (cumulative fraction of the total variation of the *Ys* that can be predicted by all extracted components). These values have to be as high as possible, and with root mean-square errors of calibration and cross-validation, *RMSEC* and *RMSECV*, respectively, have to be as low as possible, with the lowest difference between them. Low value of *RMSEC* is desirable but if the high values of *RMSECV* are present at the same time, it indicates the poor predictability of the calibration model[33].

Results and discussion

The carbamate and urea are important chemical moieties which can be seen in the molecular scaffold of a large number of biologically active molecules. Continuing our interest in carbamate and cyclic urea derivatives, the 13 compounds from our "laboratory collection"[15] depicted in Figure 2, were selected for their biological evaluation. Upon the attentive survey of literature, we concluded that data on anti-α-Gls and antiproliferative activities of compounds **1**–**13** cannot be found in literature.

These derivatives were synthesised by using the modified Hofmann rearrangement method, as we recently reported[15]. Briefly, *β*-amino carboxamides **1a**–**5a** diastereoselectively yielded cyclic ureas **1**–**5**, while various aliphatic and aromatic carboxamides **6a**–**13a** were converted to the corresponding methyl or benzyl carbamates **6**–**13**, using *N*-bromoacetamide and $LiOH{\cdot}H_2O$ in MeOH or BnOH.

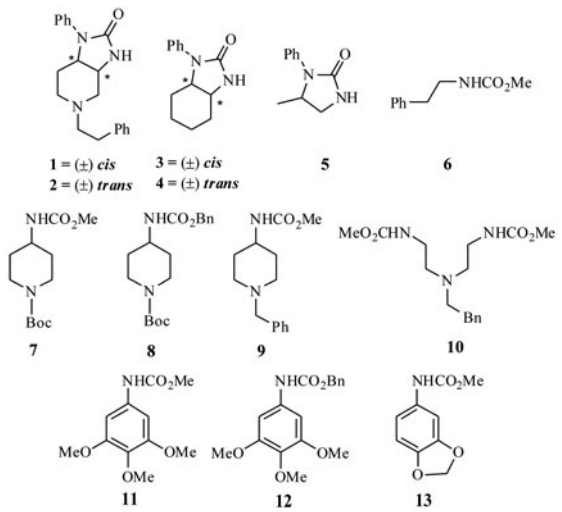

Figure 2. Structures of cyclic urea **1**–**5** and carbamate **6**–**13** derivatives.

Anti-α-*Gls* activity

The anti-α-Gls activity study showed that tested compounds expressed significant activity (Table 1). The IC_{50} values of the compound concentrations were calculated from dose response curves after absorbances were read and blanks subtracted. All 13 compounds showed better anti-α-Gls activity than standard antidiabetic drug acarbose. IC_{50} ranged from 49.85 ± 0.10 μM for benzyl(3,4,5-trimethoxyphenyl)carbamate (**12**) to 104.06 ± 0.65μM for *cis* 5-phenethyl-1-phenylhexahydro-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-one (**1**). IC_{50} for acarbose was 121.01 ± 12.18 μM. The results indicated that studied compounds could be potentially used to control postprandial hyperglycemia.

In vitro cytotoxic assay

In respect to recent findings about SAR and anticancer activities of urea derivatives[34–36], *in vitro* cytotoxicity of compounds **1**–**13** was additionally tested towards selected human cancer cell lines: cervix adenocarcinoma HeLa, non-small cell lung carcinoma A549, and human breast carcinoma MDAMB-453. The cell survival rate was determined by MTT test, after 72 h of exposure to compounds[28–30]. IC_{50} was defined as the concentration of the compound inhibiting cell survival rate by 50%, compared with a vehicle-treated control cells. Cytotoxic activities of compounds **2**, **8**, **11** and **12**, as the most active ones, are shown in Table 2, while Figure 3 depicts the cytotoxic curves from MTT assay showing the survival of HeLa, A549 and MDA-MB-453, cell grown for 72 h in the presence of increasing concentrations of complexes. *Trans*-5-phenethyl-1-phenylhexahydro-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-one (**2**) showed the best cytotoxic activity (IC_{50}) against MDA-MB-453 and A549 cell lines, with 83.41 ± 1.61μM and 110.69 ± 0.85 μM, respectively. The most potent against HeLa cells was the compound **12** with the IC_{50} = 138.74 ± 8.83 μM. Generally, the cytotoxic

Table 1. IC_{50} values of anti-α-Gls activity of the compounds **1**–**13**.

Compound	IC_{50} μM*
1	104.06 ± 0.65
2	63.03 ± 2.12
3	67.59 ± 1.90
4	68.66 ± 3.02
5	67.63 ± 0.27
6	76.02 ± 5.66
7	83.46 ± 14.21
8	71.74 ± 2.90
9	77.61 ± 2.27
10	99.48 ± 0.16
11	70.41 ± 5.21
12	49.85 ± 0.10
13	75.52 ± 8.11
acarbose	121.01 ± 12.18

*Results are expressed as mean ± standard deviation.

Table 2. IC_{50} values (μM) of tested compounds against malignant cell lines.

IC_{50}*			
compounds	HeLa	A549	MDA-MB-453
2	155.63 ± 31.75	110.69 ± 0.85	83.41 ± 1.60
8	158.29 ± 6.04	155.83 ± 0.70	112.42 ± 4.91
11	194.44 ± 1.44	200.00 ± 2.37	163.59 ± 3.93
12	138.74 ± 8.28	180.13 ± 2.57	107.63 ± 4.95

*Results are expressed as mean ± standard deviation.
#The other tested compounds didn't exhibit cytotoxic activity (the highest tested concentration was 200 μM).

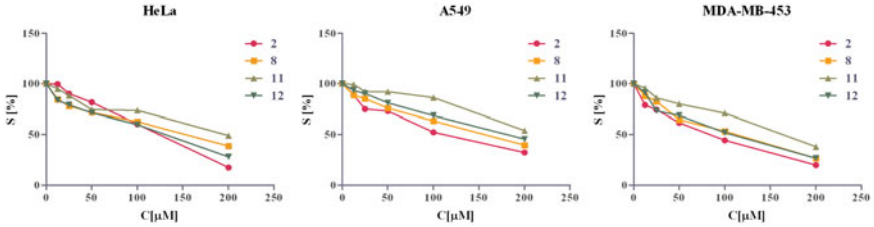

Figure 3. Cell survival rate diagram of compounds show survival of HeLa, A549 and MDA-MB-453 cells grown for 72 h in the presence of increasing concentrations of investigated compounds.

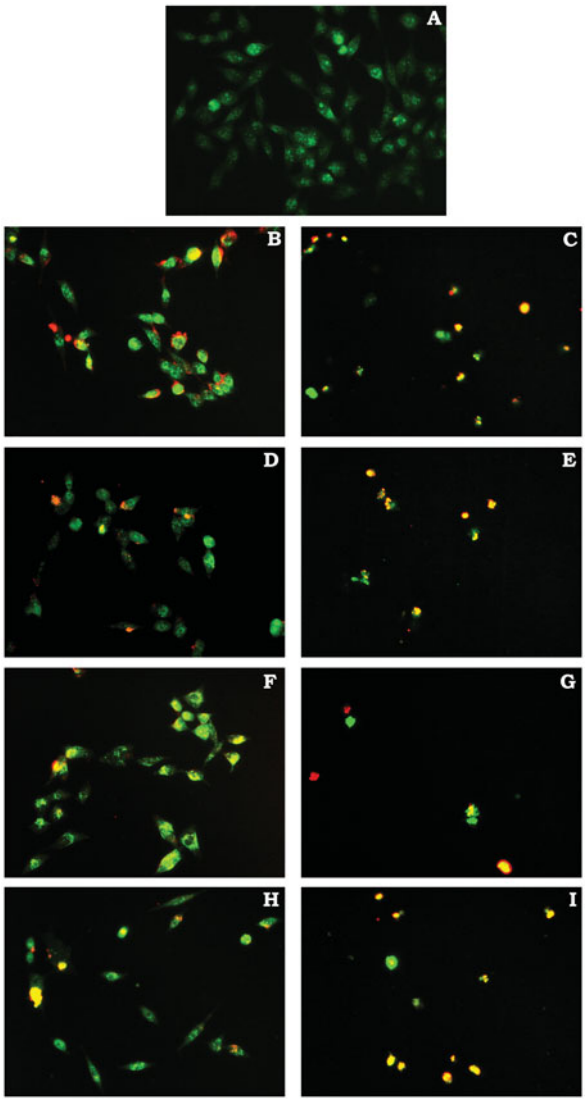

Figure 4. Morphological changes observed on HeLa cells after 24 hours treatment with IC_{50} and $2 \times IC_{50}$ concentrations of compounds dilutions. (A) Control; (B) IC_{50}, (C) $2 \times IC_{50}$ (supernatant) compound **2**; (D) IC_{50}, (E) $2 \times IC_{50}$ (supernatant) compound **8**; (F) IC_{50}, (G) $2 \times IC_{50}$ (supernatant) compound **11**; (I) IC_{50}, (H) $2 \times IC_{50}$ (supernatant) compound **12**; fluorescent microscope (PALM MicroBeamsystems, Carl Zeiss, 20×)

activities of these four compounds were considered to be moderate to low. All other compounds from the examined series were inactive regarding all three studied cell lines, meaning they did not exhibit cytotoxic activities as the IC_{50} was higher than the highest concentration tested (200 μM; data not shown).

The most active compounds (**2**, **8, 11** and **12**) were further tested to evaluate cell death type on the HeLa cells under the fluorescent microscope. Morphological changes were observed after cells were stained with acridine orange and ethidium-bromide. Acridine orange can penetrate into the living cells and emits green fluorescence, while ethidium-bromide enters the cells after cell membrane damage and emits red fluorescence. The changes of the cells morphology after 24 hours of treatment of IC_{50} and $2 \times IC_{50}$ dilutions of compounds **2**, **8, 11** and **12**, as well as untreated control are shown on the Figure 4. Observed control cells are with unchanged morphology, stained green. Morphology of the cells treated with IC_{50} dilution of the compounds **2**, **8, 11** and **12** (left side of the image) was changed, and late apoptotic signs can be observed: shrinkage of the cells, condensation of nuclear chromatin, and apoptotic bodies. On the right side of the image we can observe necrotic changes to the HeLa cells (red stained) when they have been treated with $2 \times IC_{50}$ concentrations of compounds **2**, **8, 11** and **12**. Morphological evaluation of the cell death indicated that these compounds have apoptotic effect on the cells, and therefore should be a starting point for further structural modifications in order to obtain more potent compounds.

Modeling of biological activity

Quantitative structure–activity relationship (QSAR) studies relate different molecular descriptors with their biological activities. Molecular descriptors quantitatively encode the various molecular features. They describe constitutional, topological, geometrical, electrostatic, and quantum chemical characteristics of molecules. The number of atoms and bonds in each molecule are connected to the constitutional descriptors, the atomic connectivity in the molecule to the topological descriptors, and the size of the molecule to geometrical descriptors. The electrostatic descriptors reflect characteristics of the charge distribution of the molecule, and the quantum chemical descriptors describes binding and formation energies, partial atom charge, dipole moment, and molecular orbital energy levels[37]. PLS (Partial Least Square) regression analysis is a commonly used statistical technique for performing multivariate calibration with the ability to analyse data sets with a larger number of predictor variables than objects and in situations where there is more than one dependent variable[38]. In order to derive PLS model which could help us in better understanding the mechanism of action of cyclic ureas and carbamates (**1**–**13**), the biological activity expressed as logarithm of mean concentration of two measurements were used as dependent variables and molecular descriptors as the independent ones.

PLS modeling was performed on a large number of molecular descriptors. Descriptors with variable importance in projection scores (VIP) lower than 1 which are considered as irrelevant were excluded from this set of molecular descriptors. Then, the final PLS model was built only with descriptors with the VIP scores higher than 1.

Compound **1** which showed the lowest anti-α-Gls activity was excluded as the regression outlier. The obtained PLS model was

Table 3. Statistical performance of the final PLS model.

Statistical performance of the model				Molecular descriptors included in PLS model
R^2_{cal}	R^2_{CV}	*RMSEC*	*RMSECV*	
0.901	0.680	0.021	0.041	ClQPlogS(+), FISA(+), Percent Human Oral Absorption(−), QPlogKp(−), QPlogPo/w(−), IP(eV)(+), QPPMDCK(−)

statistically significant and resulted in two latent variables. The statistical results, together with the descriptors included in the final QSAR model with descending order of regression coefficients with notification of the sign of their contribution on the dependent variable are presented in Table 3. The plot of the measured versus predicted retention parameters, plot of the variables versus VIP scores, and plot of the coefficients of the model parameters are given in Figure S1A–C (Supplemental Information).

According to the obtained PLS model, the most relevant descriptors which influence the activity of examined cyclic ureas and carbamates **1**–**13** are conformation-independent predicted aqueous solubility (ClQPlogS), hydrophilic component of the total solvent accessible surface area (FISA), Percent Human Oral Absorption, predicted skin permeability (QPlogKp), predicted octanol/water partition coefficient (QPlogPo/w), PM3 calculated ionization potential (IP(eV)), predicted apparent MDCK cell permeability (QPPMDCK). MDCK cells are considered to be a good mimic for the blood–brain barrier. Molecular descriptors ClQPlogS, FISA, and IP(eV) have positive sign of regression coefficients indicating that higher these values are, the higher is their activity against α-Gls. This is in accordance with the statment that when the drug passes through the cell membrane and is found in intracellular fluid, it has to be sufficiently water-soluble to achieve polar interactions that allow their binding to the receptor site[38]. On the other hand, molecular descriptors Percent Human Oral Absorption, QPlogKp, QPlogPo/w, QPPMDCK, which encode hydrophobic interactions influence the biological activity of both cyclic ureas **1**–**5** and carbamates **6**–**13** against α-Gls in the negative manner. These descriptors are usually positively correlated with the lipophilicity of the compound which influences the passage of molecules through the cell membrane.

The obtained QSAR model can help us better understanding the mechanism of action of examined cyclic ureas **1**–**5** and carbamates **6**–**13**. These results can qualitatatively indicate the descriptors that play an important role in the activity exhibited by similiar compounds. From this preliminary model, we can assume that in future synthesis of new compounds, the increase of their lipophilicity should be avoided, while on the other hand, introducing the subsituents capable of participation in polar interactions with active site on receptors into different positions of molecular structure would most likely enhance their activities.

Conclusions

In summary, the selected cyclic urea and carbamate derivatives **1**–**13** expressed significant *in vitro* inhibitory activity in the anti-α-Gls activity study. All studied compounds showed higher anti α-Gls activity (IC_{50} values from 49.85 ± 0.10 to 104.06 ± 0.65 μM) than the standard antidiabetic drug acarbose. Benzyl(3,4,5-trimethoxyphenyl)carbamate (**12**) was the most potent (IC_{50} = 49.85 ± 0.10 μM) when compared to acarbose (IC_{50} = 121.01 ± 12.18 μM).

In vitro cytotoxic study of compounds **1**–**13** toward three human cancer cell lines, HeLa, A549 and MDA-MB-453 indicated moderate activities of compounds **2**, **8**, **11** and **12**. Amongst them *trans*-5-phenethyl-1-phenylhexahydro-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)-one (**2**) was the most active against MDA-MB-453 cells (IC_{50} = 83.41μM). The other tested compounds expressed no activity. Moreover, morphological evaluation of cells under the fluorescent microscope revealed that apoptosis occurred after cancer cells were treated with IC_{50} concentrations of four, the most active compounds (**2**, **8**, **11** and **12**), hence they should be further investigated in the sense of structural modifications and cytotoxic activity enhancement.

QSAR analysis was attempted on activity against α-Gls by applaying PLS analysis. Obtained results qualitatively indicate the descriptors playing an important role in the activity exhibited by similiar compounds, thus suggesting that introduction of substituents able to form polar interactions with binding sites of receptor while maintaining the lipophilicity would lead us to more active structures, and thus helping us for planning the future synthesis.

This study demonstrated the promising anti-α-Gls activity of cyclic ureas and carbamates. These derivatives will be the starting point for synthesis of new analogues which will be further tested as potential antidiabetic drugs.

Disclosure statement

The authors report no declarations of interest.

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