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Synthesis, *in vitro* and *in vivo* evaluation of 2-aryl-4*H*-chromene and 3-aryl-1*H*-benzo[*f*]chromene derivatives as novel α-glucosidase inhibitors

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ABSTRACT

Herein we report a study of novel arylchromene derivatives as analogs of naturally occurring flavonoids with prominent α-glucosidase inhibitory properties. Novel inhibitors were identified via simple stepwise in silico screening, efficient synthesis, and biological evaluation. It is shown that 2-aryl-4H-chromene core retains pharmacophore properties while being readily available synthetically. A lead compound identified through screening inhibits yeast α-glucosidase with IC_{50} of 62.26 μM and prevents postprandial hyperglycemia in rats at 2.2 mg/kg dose.

Diabetes mellitus is a metabolic disorder of heterogeneous etiology mainly characterized by chronic hyperglycemia and impairment of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1] The prevalence of this disease has been steadily increasing in recent years. Specifically, in 1980 number of patients was estimated at 108 million worldwide, and in 2014 it increased to 422 million, and among people over 18 years old from 4.7% to 8.5%.[2] Type 2 diabetes, i.e. non-insulin-dependent diabetes mellitus, comprises more than 90% of all cases. It is widely accepted that hyperglycemia is one of the main drivers of metabolic memory, which in turn increases cardiovascular risk – the primary cause of diabetes-associated mortality.[3–6]

There are several clinically approved classes of drugs to improve glycemic control in diabetic patients, including oral α-glycosidase inhibitors. α-Glucosidase is an exoenzyme that hydrolyzes α-1,4-bonds at the non-reducing end of α-1,4-glycans, cleaving glucose in α-form. Substrate specificity is broad and includes maltose, malto-oligosaccharides, sucrose, amylodextrins, amylose, amylopectin, and glycogen.[7] The principle of action of α-glucosidase inhibitors is based on competitive inhibition of the enzyme and slowing the release of glucose from complex carbohydrates, which leads to a decreased postprandial hyperglycemia.[8] Currently, there are 3 drugs that have been approved for clinical use: acarbose, miglitol, voglibose. The need for new drugs of this class is due to the side effects of existing ones: limited hypoglycemic activity compared with metformin and sulfonylurea derivatives, and dyspepsia due to the fact that carbohydrates, which are not subjected to enzymatic hydrolysis, cause fermentation in the large intestine, especially in case of low compliance to a prescribed diet, thus reducing adherence to the therapy.[9]

In our previous work,[10] we investigated a series of synthetic 2-acylbenzofuranes as α-glucosidase inhibitors with *in vivo* antihyperglycemic activity. On the other hand, chromenes attract attention as a valuable source of compounds with various types of biological activity.[11] Nowadays there are many attempts to identify inhibitors of α-glucosidase among this class of compounds, which is explained by their wide presence in medicinal and dietary plants, low toxicity and antioxidant properties.[12–14] One of the main research areas of our group is the development of new synthetic routes to 4*H*-chromenes.[15–17] In the present study, we selected 2-phenyl-4*H*-chromene derivatives for this reason, and, most importantly, due to their similarity with substances commonly found in plants – flavonoids, generally with 2-phenylchromene or flavan units.

Fig. 1 shows the structure of a naturally occurred flavan derivative (+)-catechin, which inhibits α-glucosidase with IC_{50} of 53.8 μM.[18] Target compounds were designed by molecular hybridization to afford substituted 2-aryl-4*H*-chromenes, which could also be considered as products of dehydration of the corresponding phenylchromane derivatives. This modification leads to the disappearance of two

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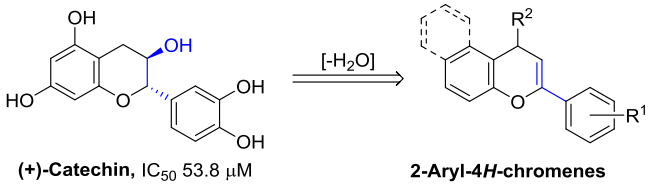


Fig. 1. Design of the target compounds from the known α-glucosidase inhibitor (+)-catechin.

stereocenters, which greatly simplifies the synthesis and purification of the target compounds. At the same time, the inhibitory activity of 2-aryl-4*H*-chromenes has not been described in the literature. Thus, the purpose of this work is to evaluate derivatives of 2-aryl-4*H*-chromenes as synthetically available potential inhibitors of α-glucosidase.

Considering current trends in the field and the collection of available compounds, we have prepared a library of potential α-glucosidase inhibitors comprising different types of scaffolds and substituents. Next, we performed similarity search with the 2-phenylchromene structure as a query employing FragFP molecular descriptor implemented in OSIRIS DataWarrior 4.7.2.[19] Similarity threshold was set to 70% in order to explore broader chemical space and to possibly identify novel types of inhibitors. As a result, a set of structurally relevant compounds was selected for evaluation via experimental biological approaches.

Target 4*H*-chromene derivatives **6** and **7** were synthesized in two steps from 1-(2-oxo-2-arylethyl)pyridin-1-ium bromides **1a-f** and 2-[acetoxy(phenyl)methyl]phenyl acetate (**2**) or 2-naphthol derivatives **4a-e** with subsequent reductive rearrangement of formed arene-condensed dihydrofurans **3** and **5** as shown in Scheme 1.

A series of dihydroarenofurans **3** and **5** were obtained from equimolar amounts of *in situ* generated pyridinium ylides $\mathbf{1}_{yl}$ and *ortho*-quinone methide $\mathbf{2}_{QM}$ and $\mathbf{4}_{QM}$ precursors via previously described thermally initiated formal [4 + 1]-cycloaddition of these species.[20] For selected recent reviews on the chemistry of *o*-quinone methides, see.[21–23] The successful synthesis of 2,3-dihydrobenzofurans **3** can be achieved by reaction of 2-(acetoxy(phenyl)methyl)phenyl acetate (**2**) as an *o*-quinone methide $\mathbf{2}_{QM}$ precursor and 1-(2-oxo-2-arylethyl)pyridin-1-ium bromides **1a,b** in the presence of 2 equivalents of DBU. The use of diacetate **2** allows to reduce the temperature of generation of highly reactive *o*-quinone methide $\mathbf{2}_{QM}$ and carry out the synthesis already in boiling acetonitrile with good yields. At the same time, the use of more accessible *o*-hydroxybenzyl alcohols or 2-[(dimethylamino)methyl] phenols usually requires a higher temperature, for example, the temperature of boiling DMF. These harsher conditions enhance side reactions and decrease the yields of the target compounds. Generation of *o*-naphthoquinone methides $\mathbf{4}_{QM}$ can be carried out in boiling acetonitrile without modifying the structures of starting 1-[(dimethylamino)methyl]naphthalen-2-ols **4a-e** due to their conjugation stabilization; their reaction with pyridinium salts **1a-d** in the presence of base (1 eq. of DBU or TMG) led to 1,2-dihydronaphtho[2,1-*b*]furans **5** with high yields. However, with pyridinium salts **1e,f** we have avoided the use of a base to increase the yields of products, but the absence of a base leads to an increase in the reaction time. In all cases, we obtained exclusively *trans*-diastereomers of corresponding dihydrofurans **3** and **5**.

For the transformation of intermediate dihydrofurans **3** and **5** into target 4*H*-chromenes **6** and **7**, we have selected previously reported reductive rearrangement under the action of zinc in acetic acid.[24] It should be noted that the rearrangement of 3-aryl-2,3-dihydrobenzofurans and 1-aryl-1,2-dihydronaphtofurans (**6a,b**, **7b-f,h**) requires longer reaction time than the 1-unsubstituted 1,2-dihydronaphtofurans. We have also found that the reaction of dihydrofuran **5i** under these conditions but with prolonged heating leads to a mixture of expected 4*H*-chromene **7i** and the product of its further reduction – chroman **7j**, which we have also examined as an inhibitor of α-glucosidase.

Once in hand, target compounds were screened against α-glucosidase in the *p*-nitrophenyl-α-D-glucopyranoside assay.[10] In preliminary fixed-time experiments, we have determined K_m for *p*-nitrophenyl-α-D-glucopyranoside as 0.1166 μM. Substrate concentration in all screening experiments was fixed to 1 mM, i.e. [S] > > K_m, to ensure enzyme saturation and to facilitate identification of non-competitive inhibitors. Efficacy of the compounds was identified at 1 mM concentration. Next, we studied the potency of hit compounds in 10^{-3}–10^{-9} molar range in order to determine IC_{50} values. Screening data is shown in Table 1. Five of the selected compounds showed significant activity (inhibition of α-glucosidase activity by more than 50% at 1 mM concentration). Next, we have studied concentration-dependent inhibition of the enzyme activity and determined IC_{50} values by nonlinear regression.

Initially, we concentrated our efforts on studying the α-glucosidase inhibitory activity of 3-aryl-1*H*-benzo[*f*]chromenes **7**, as the closer structural analogs of the previously identified inhibitor – 1,2-dihydronaphtho[2,1-*b*]furan derivative **A**.[10] Only chromenes **7d**, **7f**, **7 g** showed satisfactory results in preliminary fixed-time experiments; however, their IC_{50} values were higher than that of acarbose (Table 1). Further, we studied non-condensed 4*H*-chromenes as α-glucosidase inhibitors and surprisingly found that 2,4-diphenyl-4*H*-chromene (**6a**) is the most active derivative in the series. Interestingly, its close 4-chloro-substituted analog **6b** is nearly 15 times less potent. Another structure-activity trend could be derived for 3-aryl-1*H*-benzo[*f*]chromene derivatives. Compound **7f** comprises 4-chlorophenyl substituent in *ortho*-position to oxygen and exhibits similar activity level with *para*-4-chlorophenyl substituted **6b**, suggesting that chromene core could adopt alternative orientations in the binding site, and oxygen atom has a slight influence on affinity. Methoxy group have a negative impact on inhibitory activity, rendering compounds **7d** and **7 h** less potent. Moreover, 3-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*f*]chromene (**7j**) was found to be inactive.

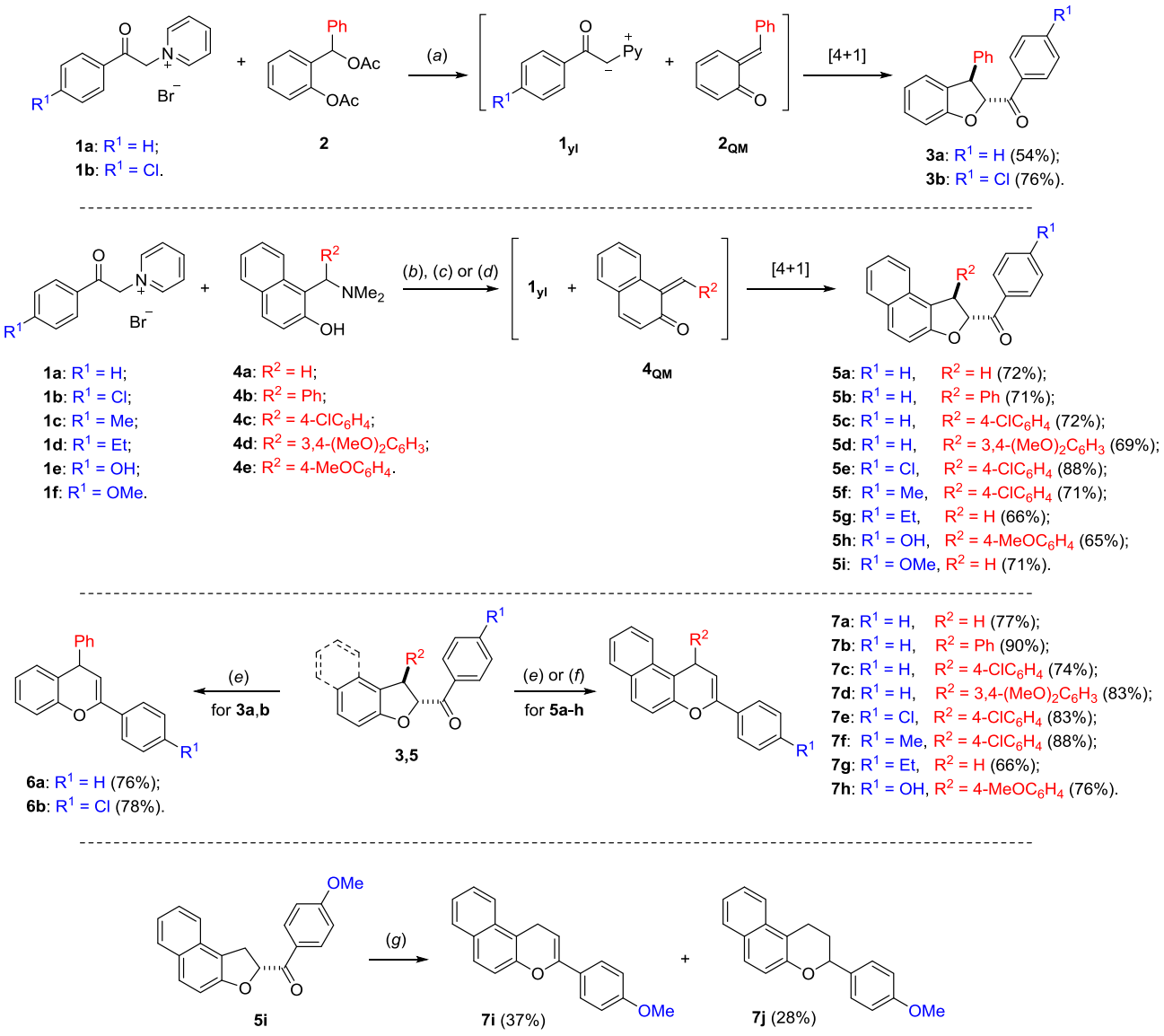
In summary, we have identified compound **6a** as a potent α-glucosidase inhibitor (nearly 9 times more active compared to acarbose). Derivatives **6b**, **7f,** and **7 g** were found to be moderate inhibitors inferior to acarbose.

A molecular modeling study was performed to elucidate amino acid residues contributing to inhibitor binding. Crystallographic structure of *S. cerevisiae* α-glucosidase is unavailable to date. The SWISS-MODEL template library[25] (SMTL version 2018-05-23, PDB release 2018–05-18) was searched with BLAST[26] and HHBlits[27] for evolutionarily related structures matching the sequence of the target enzyme (*S. cerevisiae* MAL12; Uniprot AN P53341). For details on the template search, model building and quality evaluation, see Supplementary data. Overall 1207 templates were found. Two templates of isomaltase from *S. cerevisiae* (PDB IDs 3AXH[28] and 3AJ7[29]) share the highest rank with 72% sequence identity with the target. Next, we used them as templates to build a homology model. Finally, the 3AJ7-based model was selected after final evaluation based on higher crystallographic resolution (1.30 Å) and estimated model quality. Backbone torsion analysis confirmed that 97.4% of residues are in favored regions, 2.4% are in allowed regions, and Ser281 is the only outlier. Hence, the validity of the model was confirmed.

Several studies show that flavonoids inhibit α-glucosidase in a non-competitive manner, but the corresponding allosteric site remains experimentally undefined.[30–32] Therefore, the whole enzyme molecule was targeted for molecular docking of newly identified inhibitors. We investigated the binding of **7da** and *(R)*- and *(S)*-enantiomers of **6a** and **7cc**. As a result, three plausible binding sites were identified (Fig. 3a).

Taking into account aromatic nature of inhibitors, it is not surprising that stacking interactions with tryptophan, phenylalanine and tyrosine side chains drives their binding. The abundance of aromatic amino acids is especially evident for sites A and B. Considering binding energy estimations, consistent ligand-protein interaction pattern, and proximity to the catalytic center, site A could be prioritized.

As exemplified in Fig. 2a, *(R)*-enantiomer of **6a** is predicted to be



Scheme 1. Synthesis of dihyrdoarenofurans **3** and **5**, 2-aryl-4*H*-chromenes **6a,b** and 3-aryl-1*H*-benzo[*f*]chromenes **7a–j**. *Reagents and conditions*: dihyrdoarenofurans were synthesized b previously (**5b,e,f**)[20] or according to modified procedures: (*a*) 2 eq. DBU, MeCN, Δ, 8 h, argon atmosphere (**3a,b**); (*b*) 1 eq. DBU, MeCN, Δ, 4 h, argon atmosphere (**5a,c,d,g**); (*c*) DMF, 90 °C, 17 h, argon atmosphere (**5 h**); (*d*) MeCN, Δ, 10 h, argon atmosphere (**5i**); (*e*) Zn, AcOH, Δ, 4 h (**6a,b**, **7b-f,h**); (*f*) Zn, AcOH, Δ, 2 h (**7a,g**); (*g*) Zn, AcOH, Δ, 5 h (**7i,j**).

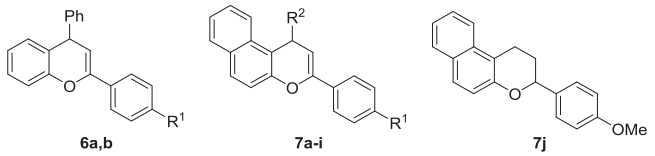
effectively buried in hydrophobic cavity of site A. It is mainly stabilized by edge-face π-π interactions of aromatic cores with Trp323 and Trp576 and π-alkyl interaction with a Leu320 side chain. Additionally, 4-phenyl substituent contributes to binding by π-π stacking with Phe318, which could be beneficial comparing to natural flavonoids. It is of interest that chlorine-substituted analogs **6b** and **7cc** are less potent, indicating that there is a limit of allowed hydrophobicity for the ligand. We could hypothesize that chlorine atom extends to a solvent accessible area thus creating desolvation penalty in energy, which is not compensated by additional interactions with the enzyme.[33] As it has been proposed from activity data, oxygen atom lacks specific interactions with the enzyme and thus could serve as solubility enhancer.

Rat and human intestinal maltase-glucoamylase have 82% sequence identity. Therefore, results obtained with the rat enzyme could be projected to human clinically relevant target. Employing the procedure described above we have built a homology model of maltase-glucoamylase from *Rattus norvegicus* (UniProt AN D3ZTX4) using X-ray derived structure of human maltase-glucoamylase as a template (PDB ID 3TOP[34]). Docking simulations performed for enantiomers of **6a** revealed only one possible binding site (Fig. 2b). It is shown that aromatic 4*H*-chromene core establishes effective π-cation and π-anion interactions with side chains of Arg1578 and Glu1583. The same is evident for Glu1690 and 4-phenyl moiety. 2-Phenyl substituent forms *T*-shaped stacking with Trp1692. Additionally, hydrophobic interactions are observed with Pro1601 and Glu1690.

Promising results encouraged us to further evaluate **6a** in an animal study. In order to confirm the potential of **6a** as an oral antidiabetic agent, we have assessed its activity in oral maltose tolerance test, which is a standard in the field.[35] Male Wistar rats were treated with 5 mg/kg acarbose or equimolar 2.2. mg/kg dose of **6a** *per os* followed with 2 g/kg maltose. Compound **6a** effectively prevented hyperglycemia associated with maltose challenge, thus confirming inhibition of rat intestinal maltase-glucoamylase activity (Fig. 3). In accordance with *in vitro* observations, the efficacy of **6a** was significantly superior to acarbose at 90 and 120 min. after maltose administration.

Thus, we have found that α-glucosidase inhibitory activity is characteristic for the 2,4-diphenylchromene derivatives as well as for their natural flavan analogs. Target compounds were efficiently synthesized

Table 1
Activity of the target 2-phenylchromene derivatives against α-glucosidase from *S. cerevisiae*.



Comp.	R^1	R^2	Inhibition at 1 mM, m ± SEM (%)	IC_{50} (μM)
6a	H	–	60.84 ± 3.79*	62.26
6b	Cl	–	68.95 ± 3.75*	950.3
7a	H	H	10.77 ± 4.09	n.d.[a]
7b	H	C_6H_5	39.59 ± 3.31	n.d.
7c	H	4-ClC_6H_4	18.26 ± 1.51	n.d.
7d	H	3,4-$(MeO)_2C_6H_3$	43.71 ± 0.67*	> 1000
7e	Cl	4-ClC_6H_4	14.86 ± 0.11*	n.d.
7f	Me	4-ClC_6H_4	47.65 ± 8.50*	897.7
7 g	Et	H	91.66 ± 4.54*	648.8
7 h	OH	4-$MeOC_6H_4$	36.08 ± 6.42	n.d.
7j	–	–	19.70 ± 5.78[d]	n.d.
Acarbose	–	–	55.78 ± 1.51*	543.6

[a] Not determined.
* Statistically significant vs. negative control, $p < 0.05$ (Student *t*-test).

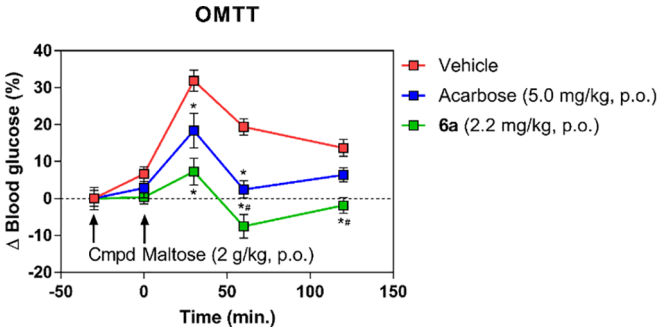


Fig. 3. Oral maltose tolerance test performed with **6a** and acarbose in male Wistar rats (m ± SEM, n = 5). $^{*}p < 0.05$ vs. vehicle; $^{\#}p < 0.05$ vs. acarbose (1-way ANOVA).

from pyridinium ylides and *ortho*-quinone methide precursors via thermally initiated formal [4 + 1]-cycloaddition and subsequent reductive rearrangement of intermediate dihydrofurans. We have identified lead compound **6a** (IC_{50} 62.26 μM), which shows better potency than acarbose *in vitro* and has promising antihyperglycemic activity in rats. Hence, derivatives of 2-aryl-4*H*-chromene represent a promising class for identifying novel α-glucosidase inhibitors for type 2 diabetes mellitus.

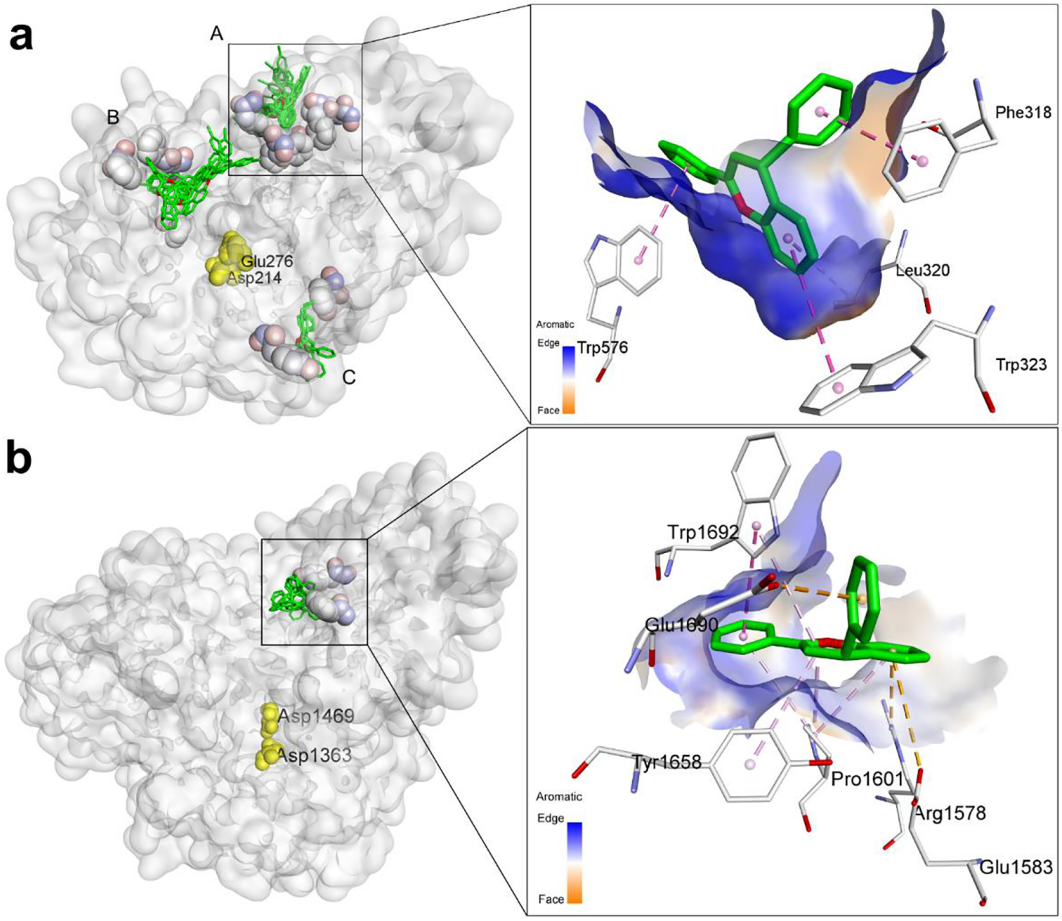


Fig. 2. Superimposed predicted binding modes for inhibitors **6a**, **7cc,** and **7da** in a homology model of α-glucosidase from *S. cerevisiae* (a) and *R. norvegicus* (b). Aromatic amino acids within 4 Å from binding sites are indicated. Catalytic residues are shown in yellow. The detailed view is shown for *(R)*-**6a** (green carbons). Key amino acids are shown in white carbons. Protein-ligand interactions are indicated with dashed lines. Binding site surface is visualized and colored according to the orientation of aromatic residues.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2018.10.018.

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