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Influenza antiviral activity of F- and OH-containing isopulegol-derived octahydro-2*H*-chromenes

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ABSTRACT

We synthesized fluoro- and hydroxy-containing octahydro-2*H*-chromenes by the Prins reaction starting from a monoterpenoid (–)-isopulegol and a wide range of aromatic aldehydes in the presence of the $BF_3 \cdot Et_2O/H_2O$ system acting as both an acid catalyst and a fluorine source. Activity of the produced compounds against the influenza A/Puerto Rico/8/34 (H1N1) virus was studied. The highest activity was demonstrated by fluoro- (**11i**) and hydroxy-containing (**10i**) derivatives of 2,4,6-trimethoxybenzaldehyde. The most pronounced virus-inhibiting effect of compounds **10i** and **11i** was observed at an early stage of infection. These compounds were supposed to be capable of binding to viral hemagglutinin, which is an agreement with data on the effect of compounds **10i** and **11i** on the viral fusogenic activity as well as by molecular docking studies.

Seasonal influenza is the most common human infectious disease resulting in approximately 3–5 million cases of severe acute lower respiratory tract infection and about 250,000 to 500,000 deaths worldwide annually, thus posing a serious public health impact.[1,2] The most effective strategy available for preventing and controlling influenza is the use of vaccines. Along with vaccination, chemotherapy is an important method for the prevention and treatment of viral diseases, especially for immunocompromised patients and during pandemics when a new virus spreads much faster than vaccine is produced and epidemically significant population groups are immunized. The currently marketed anti-influenza medications approved by FDA consist of drugs from 3 classes: amantadine and rimantadine, which are M2-ion channel blockers; oseltamivir, zanamivir, laninamivir and peramivir, which target influenza neuraminidase; and baloxavir marboxil - cap-dependent endonuclease (CEN) inhibitor.[2,3] However, the adamantanes are globally no longer recommended for clinical use because of widespread resistance among circulating influenza A viruses.[4] Influenza virus can also develop resistance to other types of drugs, including the emergence of oseltamivir-resistant strains.[5] The development of drug-resistant influenza virus mutants can be prevented by using a combination of two or more agents with different mechanisms of action.[6] Hence, it is necessary to search for novel anti-influenza agents belonging to new structural types, including those whose targets and mechanisms of action differ from the currently used ones.

Natural compounds including monoterpenoids that are components of natural essential oils are important source of novel anti-influenza agents.[7,8] Earlier, we discovered anti-influenza A (H1N1) virus activity of several compounds with a hydro-2*H*-chromene scaffold, which were synthesized by the Prins reaction using *p*-menthane alcohols and carbonyl compounds; montmorillonite *K*10 or a nanosized halloysite catalyst were used as the reaction catalysts. For example, chromenols **2** and **3** produced from an available monoterpenoid alcohol (–)-isopulegol **1** and aliphatic symmetric ketones, such as acetone and cyclopentanone,[9,10] demonstrated high activity in combination with low toxicity against the influenza virus A (H1N1) (SI = 189 and SI = 96, respectively).[9] The antiviral activity was also detected for substituted 2-(thiophen-2-yl)octahydro-2*H*-chromen-4-ol **4** (SI = 25) synthesized by the reaction of (–)-isopulegol **1** with 5-bromothiophene-2-carbaldehyde (Scheme 1).[11]

Another group of compounds with a hydro-2*H*-chromene scaffold exhibiting activity against the influenza virus H1N1 was derived from diol **5**, which is synthesized from monoterpenoid (−)-verbenone **6** in

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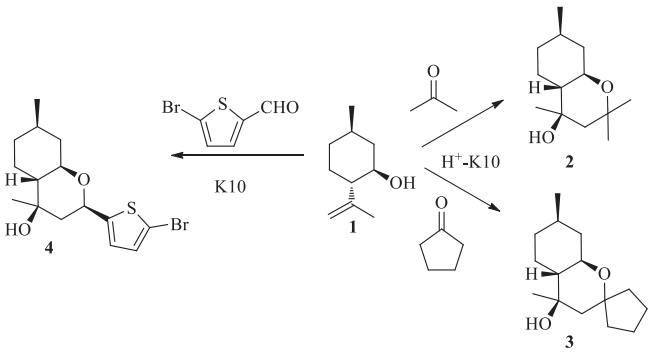
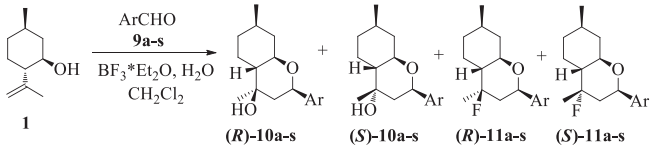


Scheme 1. (–)-Isopulegol **1** derived compounds with anti-influenza activity.[9,11.]

three stages.[12] Thus, by using starting diol **5** and aromatic aldehydes as well as the $BF_3 \cdot Et_2O/H_2O$ system as a catalyst of the reaction, we synthesized a large set of heterocyclic compounds with a hexahydro-2*H*-chromene scaffold, which contained a hydroxy group at position C-4, as well as compounds fluorinated at this position (Scheme 2). A number of substances thus obtained showed high antiviral activity, for example compound **7** with the hexahydro-2*H*-chromene framework synthesized from **5** and *p*-chlorobenzaldehyde and 2,4,6-trimetoxybenzaldehyde-derived fluorine-containing compound **8**, which combines high antiviral potency (IC_{50} = 5 μM) and low cytotoxicity with good selectivity index SI value of 55.[13]

The only examples of transformation of monoterpenoid alcohols via the Prins reaction in the presence of $BF_3 \cdot Et_2O$ reported before our work are the reactions of (–)-isopulegol **1**[14] or geraniol[15] with aldehydes; however, olefin products lacking the fluorine atom are formed in both cases (Scheme 3). At the same time, the introduction of the fluorine atom into the molecule is an important strategy in the development of new biologically active compounds, which enables changing lipophilicity and electrostatic interactions and increasing the metabolic stability of compounds[16] and, as a result, affects their physiological activity.[17–19] It should be mentioned that some of the top-selling drugs on the current pharmaceutical market contain fluorine atoms in their structures.[20] In this regard, the development of methods for introducing the fluorine atom into organic molecules and expansion of the range of fluorinating reagents available for synthetic organic chemistry are extremely important.

The purpose of this study was to develop new anti-influenza agents by combining two previously found active fragments: an octahydro-2*H*-chromene scaffold synthesized from (–)-isopulegol **1** as well as aromatic

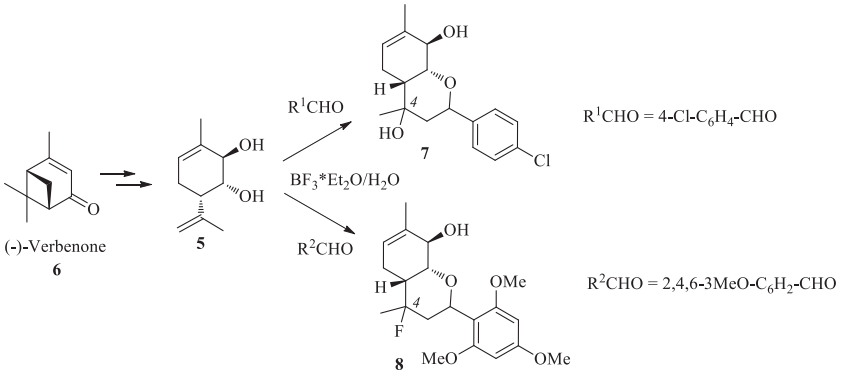


Scheme 4. Interaction of (–)-isopulegol **1** with aromatic aldehydes **9a-s** catalyzed by BF_3*Et_2O/H_2O.

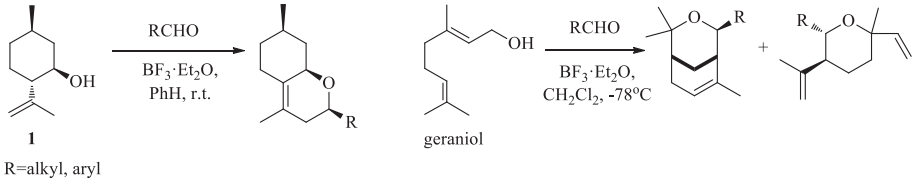
Table 1
Synthesis of compounds **10** and **11**.

	Ar	Yield[a] ((4*R*)/(4*S*))	
		10	**11**
a	C_6H_5	20% (4.5:1)	70% (0:1)
b	4-MeO-C_6H_4	14 (35:1)	58 (1:1.3)
c	2,3-MeO-C_6H_3	25% (5:1)	60% (1:1.7)
d	2,4-MeO-C_6H_3	51% (24.5:1)	35% (2.5:1)
e	2,5-MeO-C_6H_3	27% (8:1)	60% (1:1.7)
f	3,4-MeO-C_6H_3	20% (4:1)	52% (1:1.3)
g	2,3,4-MeO-C_6H_2	24% (60:1)	53% (1.7:1)
h	2,4,5-MeO-C_6H_2	35% (˃99: traces)	42% (5:1)
i	2,4,6-MeO-C_6H_2	60% (10:1)	31% (1:4)
j	3,4,5-MeO-C_6H_2	20% (4:1)	62% (1:2)
k	2-OH-C_6H_4	46% (10.5:1)	19% (0:1)
l	4-OH-C_6H_4	30% (1:0)	42% (1:1)
m	3-OH,4-MeO-C_6H_3	26% (5.5:1)	64% (1:1.5)
n	3-MeO,4-OH-C_6H_3	27% (12.5:1)	56% (1:1.2)
o	4-OH,3,5-MeO-C_6H_2	23% (6.6:1)	51% (1:1.4)
p	4-F-C_6H_4	8% (3:1)	55% (1:5.9)
q	4-Cl-C_6H_4	13% (2:1)	51% (1:8.2)
r	4-Br-C_6H_4	10% (2:1)	65% (traces:1)
s	4-NO_2-C_6H_4	25 (1:1.5)	60% (0:1)

[a] Reaction conditions: (–)-isopulegol **1** (3.3 mmol), aldehyde (3.3 mmol), BF_3*Et_2O (4.9 mmol) and H_2O (24.4 mmol)



Scheme 2. Diol **5** derived compounds with anti-influenza activity.



Scheme 3. Prince reaction of (–)-isopulegol **1** and geraniol.[14,15.]

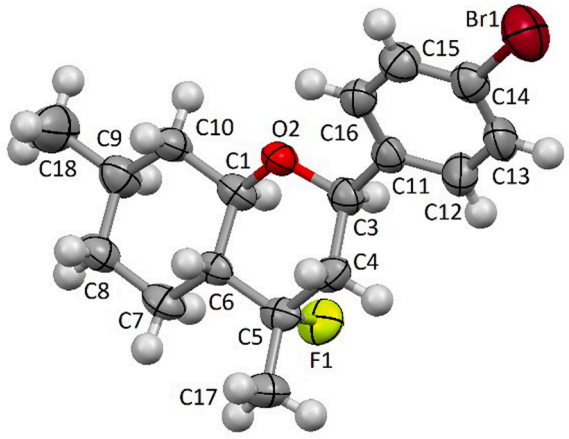


Fig. 1. Molecular structure of (4*S*)-**11r** (50% probability thermal ellipsoids are shown).

aldehyde moieties in the presence of the $BF_3 \cdot Et_2O/H_2O$ system as an acid catalyst and a fluorine source.

The synthesis of octahydro-2*H*-chromene-based compounds was carried out according to the procedure described previously[13,21] in one preparative step *via* the reaction between (–)-isopulegol **1** and aromatic aldehydes **9a-s** in the presence of $BF_3 \cdot Et_2O/H_2O$ in CH_2Cl_2 and at a temperature of 2 °C for 2.5 h within which complete conversion of (–)-isopulegol **1** was reached. The progress of the reaction was monitored by GLC. The boron trifluoride etherate acted as both an acid catalyst and a fluorine source, leading, as in the case of similar reactions of diol **5**,[13,21] to the formation of two pairs of epimers containing either hydroxy group or fluorine atom at position C-4 (**10a-s** and **11a-s**, respectively; Scheme 4). The obtained results are summarized in Table 1.

The total yield of octahydro-2*H*-chromenes **10** and **11** in the reactions was 70–90%, with the predominant formation of fluorides **11**, except reactions with 2,4-dimethoxybenzaldehyde **9d**, 2,4,5- and 2,4,6-trimethoxybenzaldehyde **9 h** and **9i**, and 2-hydroxybenzaldehyde **9 k** where the main products were compounds **10** or both types of products formed in equal amounts. The structure of isomer (4*S*)-**11r** was additionally verified by the XRD data (Fig. 1).

It should be noted that, as we showed earlier,[13,21] the reactions of diol **5** with aromatic aldehydes in the presence of $BF_3 \cdot Et_2O/H_2O$ led to the predominant formation of (*S*)-isomers with the axially located methyl group in the case of hydroxy-2*H*-chromene derivatives and (*R*)-isomers with the equatorial methyl group at C-4 in the case of fluorinated products. A similar pattern is observed for the diastereomeric distribution of 4-hydroxy-containing products **10** formed from (–)-isopulegol **1**. The major isomers of hydroxyl-containing compounds **10** are isomers with the axial methyl group, i.e. (*R*)-isomers, except reactions with 4-NO_2-benzaldehyde **9 s**. Among fluoro-2*H*-chromene derivatives **11**, the diastereomeric distribution is not unambiguous, but in most cases compounds **11** were formed mainly as isomers with the equatorial methyl group, i.e. as (*S*)-isomers.

Previously, for the reactions of diol **5** with aromatic aldehydes in the

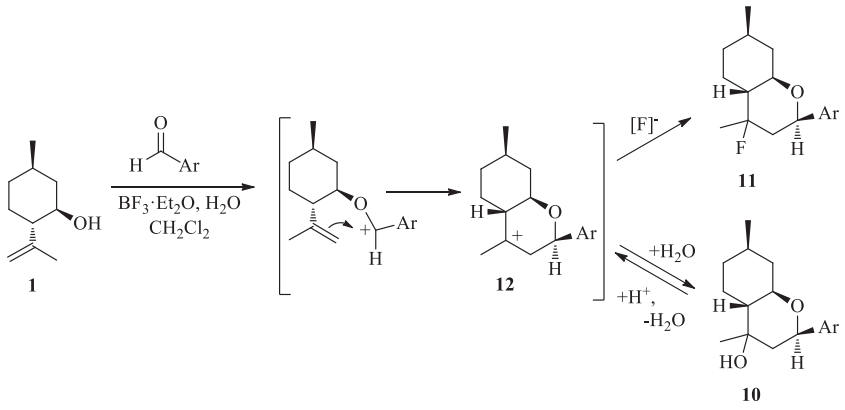
Table 2
Antiviral activity and cytotoxicity of compounds **10** и **11**.

	Ar	Compounds of type **10**			Compounds of type **11**		
		CC_{50}[a], μM	**IC_{50}**[b], μM	**SI**[c]	**CC_{50}**[a], μM	**IC_{50}**[b], μM	**SI**[c]
a	C_6H_5	580 ± 31	100 ± 11	6	65 ± 5	>38	2
b	4-MeO-C_6H_4	689 ± 45	29 ± 4	**24**	171 ± 8	>103	2
c	2,3-MeO-C_6H_3	>937	>937	1	180 ± 11	43 ± 4	4
d	2,4-MeO-C_6H_3	>937	78 ± 5	**12**	379 ± 29	155 ± 21	2
e	2,5-MeO-C_6H_3	512 ± 36	>312	2	37 ± 2	>31	1
f	3,4-MeO-C_6H_3	>937	344 ± 40	3	20 ± 2	>9	2
g	2,3,4-MeO-C_6H_2	>857	717 ± 76	1	133 ± 11	6 ± 1	**22**
h	2,4,5-MeO-C_6H_2	>857	>857	1	78 ± 5	6 ± 1	**13**
i	2,4,6-MeO-C_6H_2	856 ± 49	19 ± 2	**45**	851 ± 62	24 ± 3	**35**
j	3,4,5-MeO-C_6H_2	405 ± 24	>285	1	568 ± 46	199 ± 23	3
k	2-OH-C_6H_4	>1086	>1086	1	44 ± 3	>36	1
l	4-OH-C_6H_4	127 ± 8	87 ± 10	1	95 ± 4	>36	3
m	3-OH,4-MeO-C_6H_3	738 ± 46	118 ± 19	6	136 ± 9	>32	4
n	3-MeO,4-OH-C_6H_3	411 ± 28	>327	1	642 ± 36	>324	2
o	4-OH,3,5-MeO-C_6H_2	473 ± 31	235 ± 30	2	158 ± 11	59 ± 7	3
p	4-F-C_6H_4	65 ± 2	>36	2	68 ± 4	>36	2
q	4-Cl-C_6H_4	62 ± 2	>37	2	57 ± 4	29 ± 4	2
r	4-Br-C_6H_4	132 ± 10	>89	1	>882	391 ± 44	2
s	4-NO_2-C_6H_4	>982	393 ± 29	3	>976	>976	1
	Rimantadine	326 ± 21	69 ± 9	5			
	Ribavirin	>2130	35 ± 5	**61**			

[a] CC_{50} is the median cytotoxic concentration, i.e., the concentration causing 50% cell death.

[b] IC_{50} is the 50% inhibiting concentration, i.e., the concentration causing 50% decrease of virus replication.

[c] SI is the selectivity index, which is the CC_{50}/IC_{50} ratio. CC_{50}′s and IC_{50}′s are presented as mean ± standard deviation. The values are calculated from three independent experiments.



Scheme 5. Presumable scheme of **10** and **11** formation.

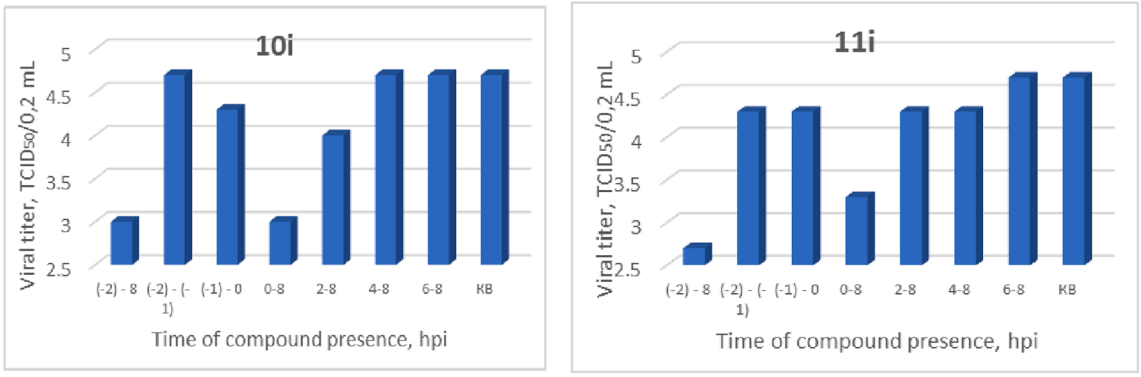


Fig. 2. Activity of **10i** and **11i** against influenza virus A/Puerto Rico/8/34 (H1N1) according to time-of-addition experiment.

presence of $BF_3 \cdot Et_2O/H_2O$, we showed that the fluoro- and hydroxy-chromene ratio may be affected by many factors, such as reaction temperature, reagent ratio (amounts of aldehyde, $BF_3 \cdot Et_2O$, water), and conversion degree of the starting diol **5**, as well as demonstrated the conversion of fluoro-chromene derivatives into hydroxy-containing analogs.[21] In addition, investigation of reactions of (–)-isopulegol **1** with thiophene-2-carboxaldehyde[22] and acetone[10] catalyzed by heterogeneous acid aluminosilicate catalysts revealed that the stereoselectivity of octahydro-2*H*-chromenol formation (ratio of (*R*)- and (*S*)-diastereomers) depended on the concentration of acid sites, reaction temperature, and initial concentrations of reagents. The produced hydroxy-compounds **10** may probably also partially convert, as we showed earlier,[21] into fluorides **11** via interaction with a fluorine source by the S_N2 mechanism or via protonation and dehydration leading to the formation of carbocation **12** (Scheme 5). Thus, to correctly understand regio- and stereoselectivity of the formation of fluoro- and hydroxy-substituted octahydro-2*H*-chromenes in each case, detailed investigation of the Prins reactions catalyzed by the $BF_3 \cdot Et_2O/H_2O$ system is required.

Thus, a large set of new compounds with an octahydro-2*H*-chromene scaffold was produced. By using silica gel column chromatography, we were able to individually isolate the main (*R*)-isomers of compounds **10b**, **10d–h**, and **10 k–p**, but could not separate diastereomers of fluorinated product **11** with the chromene scaffold. Therefore, the antiviral activity of compounds **10b**, **10d–h**, and **10 k–p** was studied for their (*R*)-isomers; the activity of compounds **11 k**, **11r**, and **11 s** was studied for (*S*)-isomers. In other cases, the biological activity was investigated for a diastereomeric mixture at ratios indicated in Table 1.

For biological testing, we used reference laboratory strain of H1N1 subtype (A/Puerto Rico/8/34). The antiviral activity of the synthesized compounds was studied by the technique described earlier.[23] Cytotoxicity of the compounds was evaluated in MDCK cells as described previously.[23] Based on the data obtained, selectivity index (SI) was calculated for each derivative. The compounds with SI = 10 and higher were considered as active.

The results of an *in vitro* study of cytotoxic and anti-viral properties of obtained compounds are summarized in Table 2.

Compound **10a** with a hydroxy group at position C-4 and an unsubstituted aromatic ring did not exhibit significant antiviral activity (Table 2). The introduction of a methoxy group into the *para*-position of the aromatic ring generally increased activity against the influenza A (H1N1) virus and decreased cytotoxicity; on the contrary, the introduction of methoxy groups into *meta*-positions reduced the antiviral effect. The role of *ortho*-methoxy groups was not unambiguous. Accordingly, the highest activity was demonstrated by compounds **10b** and **10i** with a methoxy group in the *para*-position and without *meta*-substituents, which, in combination with low cytotoxicity, resulted in good SI amounting to 24 and 45, respectively. A selectivity index of>10 was also found for compound **10d** with a methoxy group in the *para*-position but in this case a relatively high selectivity index was associated mainly with low toxicity and not with high activity. Note that previously diol **5** derivatives did not exhibit a clear dependence of the antiviral activity on the location of methoxy groups in the aromatic ring.[13] Substitution of methoxy groups in the aromatic ring by hydroxy groups, halogen atom, or a nitro group decreased the antiviral activity and/or increased cytotoxicity, which led to low selectivity indexes.

Comparison of the antiviral activity of octahydro-2*H*-chromenes **10** with that of the appropriate compounds **11** reveals that the replacement of the hydroxy substituent with a F atom in position C-4 usually leads to an increase in the antiviral activity (decrease in IC_{50}), but at the same time, there is also an increase in cytotoxicity of chromenols **11**, which generally results in low SI values. However, three fluoro-derivatives, **11 g**, **11 h**, and **11i**, having three methoxy groups in the aromatic ring

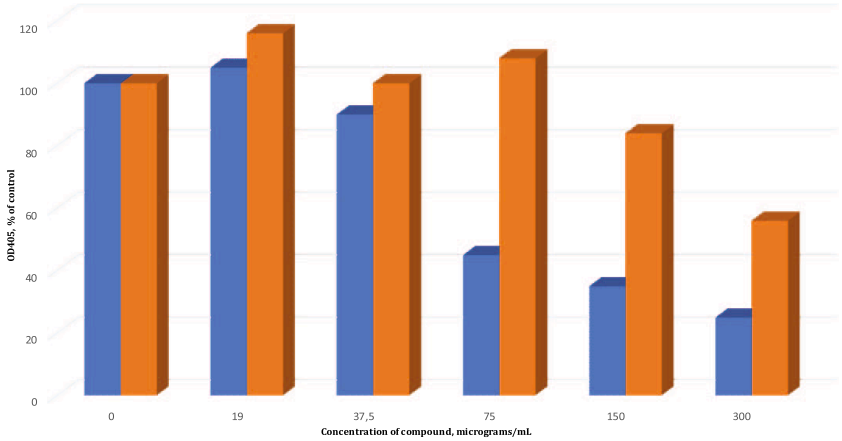


Fig. 3. Anti-fusogenic activity of **10i** (orange) and **11i** (blue) against hemagglutinin activity of influenza virus A/Puerto Rico/8/34 (H1N1).

Table 3
The docking results for compounds **10i** and **11i**. Energy characteristics are given in kcal/mol.

	HOA[a], % > 80 is high	PCaco[b], nm/*sec* > 500 is great	(*R*)-Docking score	IFD score	Interaction with amino acids	(*S*)-Docking score	IFD score	Interaction with amino acids
10i	100	4467.3	−10.0	−3041.6	K558 – π-cation stacking; K551 – H-bridge	×	×	×
11i	100	9906.0	−9.5	−3038.5	S554 – H-bridge	−8.5	−3036.4	only hydrophobic

[a] HOA – Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model;
[b] PCaco – Predicted apparent Caco-2 cell permeability in nm/*sec*. Caco-2 cells are a model for the gut-blood barrier. These predictions are for non-active transport

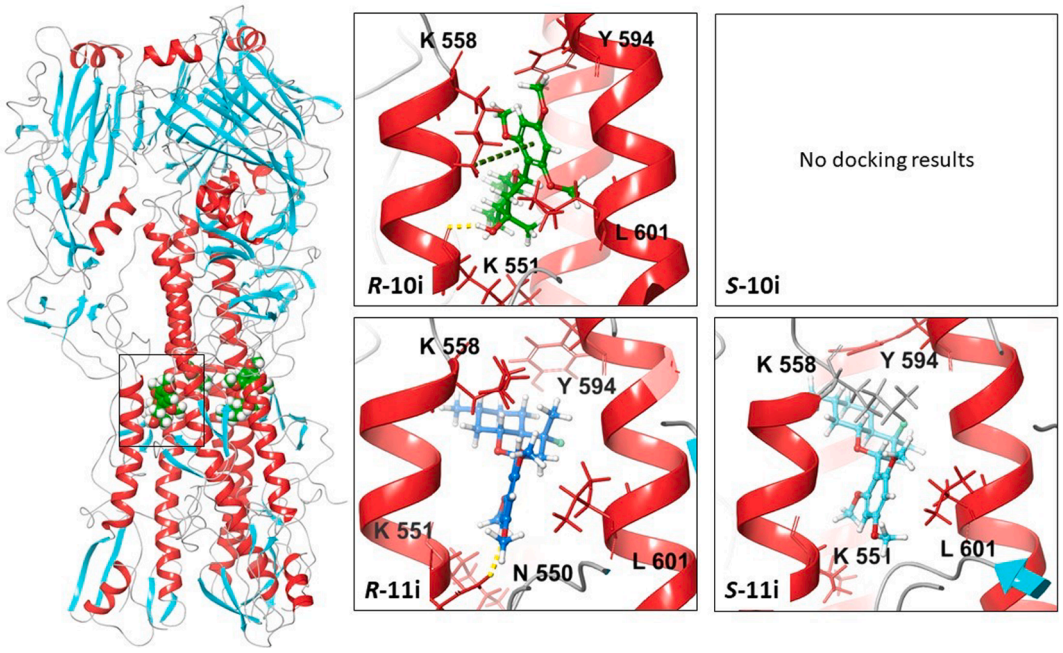


Fig. 4. Hemagglutinin and the binding site of potential inhibitors: π-cation stacking interactions are shown by the green dashed line, hydrogen bridges by the yellow line.

showed both good antiviral activity and moderate cytotoxicity, which resulted in high selectivity indexes of 22, 13 and 35, respectively.

Thus, the best selectivity indices were found for both hydroxy-octahydro-2*H*-chromene (**10i**) and fluoro-octahydro-2*H*-chromene (**11i**) derivatives synthesized from 2,4,6-trimethoxybenzaldehyde. Interestingly, fluorine-containing derivative **8**, which was produced earlier from diol **5** and 2,4,6-trimethoxybenzaldehyde **9i**, also showed significant antiviral activity.[13]

Compounds **10i** and **11i** demonstrating high anti-influenza activity and the highest selectivity index were tested for antiviral activity depending on the time of addition to infected cells. In both cases, compounds **10i** and **11i** exhibited the most pronounced virus-inhibiting activity at an early stage of infection (Fig. 2).

Previously,[9] given the activity spectrum of compound **2** against different influenza virus strains, its predominant effect at an early stage of infection, and molecular modeling, it was suggested that a potential target of the compound might be hemagglutinin enabling the virus to attach to a host cell. Taking into account the high activity of compounds **10i** and **11i** at an early stage of infection and their structural similarity to compound **2**, hemagglutinin might also be proposed as one of the potential targets. To verify this suggestion, we studied the effect of compounds **10i** and **11i** on the fusogenic activity of viral hemagglutinin.

As can be seen from the results obtained, both **10i** and **11i** demonstrate strong dose-dependent inhibiting activity against influenza virus hemagglutinin (Fig. 3).

Molecular docking of potential HA inhibitors to the binding site was performed for leader compounds **10i** and **11i** for both 4*R*- and 4*S*-diastereomers. The biological target was selected based on the results of the time of addition experiment, evaluation of the leader compound effect on the fusogenic activity of viral hemagglutinin, and previously obtained data for structurally similar compounds.[9] The docking results are shown in Table 3.

In general, affinity of the ligands is comparable. The compounds are located between two α-helices, forming a series of non-covalent interactions with the surrounding amino acids (Fig. 4). This binding of potential HA inhibitors complicates separation of α-helices and may impede further conformational transition from pre- to post-fusion.[24]

We have estimated ADME parameters, which would predict whether the synthesized compounds can be applied as medicines (for details see SI). According to calculation results (Table 3) the compounds would have 100% human oral availability and high membrane permeability. Thus, the compounds could be considered as bioavailable. Based on the calculations, it seems that the bioavailability of fluorine containing compound **11i** could be higher than that of **10i**.

Noteworthy, docking of the (*S*)-isomer of compound **10i** failed. In the case of **11i**, the (*S*)-isomer also bind poorer than the (*R*)-isomer. The docking score that characterizes binding of the (*S*)-**11i** ligand in a hydrophobic pocket and the IDF score that evaluates the total energy of the ligand–protein system exceed the values describing the interaction between (*R*)-**11i** and hemagglutinin. Thus, among the isomers, the (*R*)-stereoisomer is likely to exhibit biological activity. The (*R*)- and (*S*)-isomer ratio is 10 : 1 for **10i**; in the case of **11i**, the ratio shifts toward (*S*)-isomers and is 1 : 4 ((*R*)- and (*S*)-, Table 1). The weighted mean values characterizing affinity of **11i** for the protein, with allowance for the (*R*) and (*S*) ratios, amount to –8.7 kcal/mol (docking score) and –3036.8 kcal/mol (IFD score). Thus, **11i** is characterized by lower

affinity for the HA binding site compared to **10i**. These data correlate with the results of biological tests (Table 3), according to which **10i** inhibits the influenza virus at a lower concentration than **11i**.

Therefore, we synthesized F- and OH-containing isopulegol-derived octahydro-2*H*-chromenes and studied their activity against the influenza A/Puerto Rico/8/34 (H1N1) virus. The most active compounds were **10i** and **11i** containing a 2,4,6-trimethoxybenzyl substituent. Given the results of time addition experiments, investigation of the effect of these compounds on the viral fusogenic activity, and molecular docking, hemagglutinin is suggested as a possible molecular target.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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