In silico drug-likeness, biological activity and toxicity prediction of new 3,5-bis(hydroxymethyl) tetrahydro-4H-pyran-4-one derivatives

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This paper presents the results of predicting drug-likeness, biological activity, and toxicity for 8 new derivatives of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one using bioinformatic methods. The physicochemical and pharmacokinetic parameters of the studied compounds were determined, *in silico* screening for biological activity and prediction of their toxicity were carried out. Physicochemical and pharmacokinetic parameters were evaluated using the Molinspiration Cheminformatics service. It was found that compounds **1–11** corresponded to Lipinski's rule for drug-like compounds. As predicted in Molinspiration, compound **4** exhibits significant biological activity as a possible enzyme inhibitor and G-protein coupled receptor ligand. Compound **6** is active as an ion channel modulator. Virtual PASS screening identified compounds with potential antidiabetic activity (**1–3, 5–8**) and activity in the treatment of phobic disorders and dementias (**1–5**, **7**, **8**, **11**). Compound **1** can potentially act as a substrate for CYP2H, and inhibitors of enzymes of the peptidase group are **1**, **3**, **4**, **6**, **7**, **11**. As a result of QSAR prediction based on LD_{50} values calculated in ProTox-II, compound **10** belongs to class 6; compounds **1–3**, **5** and **8** belong to the 5th class of toxicity; compounds **6** and **9** belong to the 4th class. Compound **4** belongs to class 3. Compounds **1–9** do not exhibit the toxicities shown in the ProTox-II models. Compounds **10** and **11** may be carcinogenic.

Keywords: tetrahydropyran-4-one; bioavailability; drug-likeness; biological activity; toxicity; PASS.

In silico 3,5-бис(гидроксиметил) тетрагидро-4Н-пиран-4-онның жаңа туындыларының дәрілік қосылыстарға ұқсастығын, биологиялық белсенділігін және уыттылығын болжау

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Мақалада биоинформатикалық әдістерді пайдалана отырып, 3,5-бис(гидроксиметил)тетрагидро-*4H*-пиран-4-онның 8 жаңа туындысы үшін дәрілік қосылыстармен ұқсастықты, биологиялық белсенділікті және уыттылықты болжау нәтижелері ұсынылған. Зерттелетін қосылыстардың физика-химиялық және фармакокинетикалық параметрлері анықталды, биологиялық белсенділікке *in silico* скринингі және олардың уыттылығын болжау жүргізілді. Физика-химиялық және фармакокинетикалық параметрлерді бағалау Molinspiration Cheminformatics сервисінің көмегімен жүргізілді. Зерттелген **1-11** қосылыстары дәрілік қосылыстар үшін Липинский ережесіне сәйкес келеді. Molinspiration болжамына сәйкес, **4** қосылыс биологиялық белсенділікті фермент ингибиторы және G ақуызымен байланысқан рецепторлардың лигандасы ретінде көрсетеді. **6** қосылыс иондық канал модуляторының белсенділігін көрсетеді. PASS бағдарламасындағы виртуалды скрининг диабетке қарсы белсенділігі (**1–3**, **5–8**) және фобтық бұзылулар мен деменцияны емдеу саласындағы белсенділігі бар қосылыстарды анықтады (**1–5**, **7**, **8**, **11**). ProTox-II LD_{50}-де есептелген QSAR болжамының нәтижесінде **10** қосылыс 6 классқа жатады, **1-3, 5** және **8** қосылыстар уыттылықтың 5-класына, **6** және **9** қосылыстары 4 классқа жатады. **4** қосылыс 3 классқа жатады. **1–9** қосылыстары ProTox-II модельдерінде көрсетілген уыттылық түрлерін көрсетпейді. **10** және **11** қосылыстар канцерогенді болуы мүмкін.

Түйін сөздер: тетрагидропиран-4-он; биожетімділік, дәрілерге ұқсастық; биологиялық белсенділік; уыттылық; PASS.

In silico прогнозирование сходства с лекарственными соединениями, биологической активности и токсичности новых производных 3,5-бис(гидроксиметил) тетрагидро-4Н-пиран-4-она

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В настоящей работе представлены результаты прогнозирования сходства с лекарственными соединениями, биологической активности и токсичности для 8 новых производных 3,5-бис(гидроксиметил)тетрагидро-*4H*-пиран-4-она с использованием биоинформатических методов. Определены физико-химические и фармакокинетические параметры исследуемых соединений, проведен *in silico* скрининг на биологическую активность и прогнозирование их токсичности. Оценка физико-химических и фармакокинетических параметров проводилась с помощью сервиса Molinspiration Cheminformatics. Найдено, что исследованные соединения **1–11** соответствуют правилу Липински для лекарственно-подобных соединений. Согласно прогнозированию в Molinspiration, соединение **4** проявляет биологическую активность в качестве возможного ингибитора ферментов и лиганда рецепторов, связанных с G-белком. Соединение **6** проявляет активность модулятора ионных каналов. Виртуальный скрининг в программе PASS выявил соединения, потенциально обладающие противодиабетической активностью (**1–3**, **5–8**) и активностью в области лечения фобических расстройств и деменций (**1–3**, **7**, **8**, **11**). Соединение **1** потенциально может выступать субстратом CYP2H, а ингибиторами ферментов пептидазной группы являются **1**, **3**, **4**, **6**, **7**, **11**. В результате прогноза QSAR на основе рассчитанных в ProTox-II значений LD_{50}, соединение **10** относится к классу 6, соединения **1–3**, **5** и **8** относятся к 5 классу токсичности, соединения **6** и **9** относятся к 4 классу. Соединение **4** относится к классу 3. Соединения **1–9** не проявляют виды токсичности, представленные в моделях ProTox-II. Соединения **10** и **11** могут проявлять канцерогенность.

Ключевые слова: тетрагидропиран-4-он; биодоступность; подобность лекарствам; биологическая активность; токсичность; PASS.

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Article (Статья)

In silico drug-likeness, biological activity and toxicity prediction of new 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one derivatives

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1. Introduction

In the laboratory of al-Farabi KazNU, derivatives of 3,5-substituted tetrahydropyran-4-one **1** were obtained. The synthesis and characteristics of **1-11** are given in [1-4]. The structures of the described compounds are shown in the scheme (Figure 1).

Tetrahydropyran-4-ones and their derivatives are among the simplest, widely studied and used in medicine heterocyclic compounds [5], which are building blocks for the synthesis of compounds with biological activity [6-8]. Tetrahydropyran-4-one cycles have been found in biologically active natural compounds [9].

Modern computer forecasting tools based on available databases make it possible to investigate *in silico* the bioavailability, biological activity and toxicological properties of organic compounds of various classes. This computational approach facilitates the search for active compounds and screening of drug candidates in preclinical studies.

Unfavorable bioavailability is an important reason for the failure of drug candidates. Given the lack of experimental data on the biological activity of compounds **1–11**, *in silico* prediction seems to be an appropriate approach for the preliminary assessment of parameters such as bioavailability, biological activity, and toxicity.

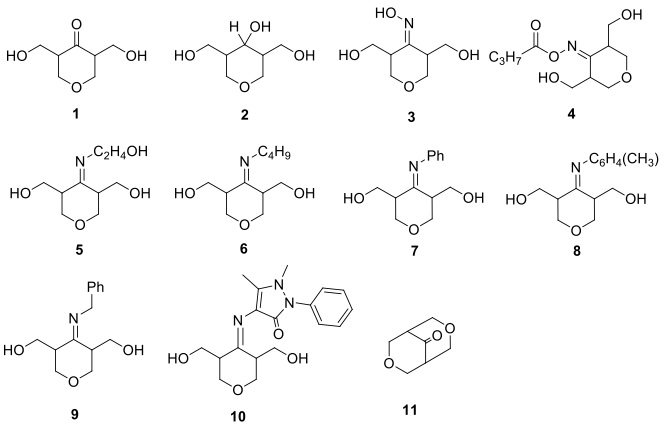

Figure 1 – Derivatives of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one

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The aim of this study is to predict the parameters of bioavailability and drug-likeness by Molinspiration Cheminformatics [10], to predict the spectra of biological activity by PASS online [11] and to calculate the toxicity by ProTox-II [12] for 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one **1** and its new derivatives **2–11**.

2. Experiment

The synthesis and identification of **1-11** are reported in [1-4]

The program Molinspiration Cheminformatics was used to calculate the topological polar surface area (TPSA), logP, molecular weight (MW), the volume of the molecule, the number of rotatable bonds (NRotB), the number of donors (ND) and acceptors (NA) of hydrogen bonds.

The prediction of biological activity of **1–11** was performed using PASS online. Chemical structures and SMILES notations were created using ACD Labs ChemSketch [13].

QSAR prediction of the toxicity for compounds **1–11** was performed using the ProTox-II service. The training set consists of 40,000 compounds; LD_{50} values were determined in experiments on mice or rats.

3. Results and discussions

3.1 Drug-likeness and pharmacokinetic properties

In order to establish the bioavailability and drug-likeness of the studied compounds, they were tested against Lipinski's "rule of five", according to which active compounds can violate no more than one of the following conditions (all numbers are multiples of 5, which explains the name of the rule) [14]: a) the number of H bond donors (the total number of N-H and O-H bonds) does not exceed 5; b) the number of H bonds acceptors (the total number of N or O atoms) does not exceed 10; c) the molecular weight must be less than 500 a.m.u.; d) *log*P (measure of lipophilicity of molecules) not higher than 5.

Lipinski's rule is used to identify drug-like compounds, although, like any rule, it allows exceptions [15–17]. But in most cases, the compliance of compounds with this rule determines their bioavailability and pharmacokinetics [18, 19]. The data in Table 1 shows that all tested compounds satisfy Lipinski's rule.

The descriptors for compounds **1–11** calculated using Molinspiration Cheminformatics are shown in Table 1.

The data in Table 1 shows that all target compounds satisfy Lipinski's rule.

In addition to Lipinski parameters, the descriptors of pharmacokinetic properties and bioavailability of molecules are the molecular polar surface area (PSA) and the number of rotatable bonds (NRotB).

PSA is defined as "the sum of the surfaces of polar atoms (usually O, N, and attached H atoms) in a molecule" [16]. This parameter correlates with the transport of compounds across membranes, which links this descriptor to human intestinal absorption and drug penetration through the blood-brain barrier. Molinspiration Cheminformatics uses PSA calculated as the topological area of the polar surface (TPSA, Table 1). The literature indicates that 'In order for molecules to cross the blood-brain barrier and act on receptors in the central nervous system, a PSA level of less than 90 Å squared is usually required. If the PSA of a molecule exceeds 140 Å squared, it will not have the ability to penetrate cell membranes" [20]. According to calculations, molecules **1–11** satisfy both requirements.

Number of rotatable bonds "is a topological parameter that is a measure of molecular flexibility. This parameter is used as a descriptor for the oral bioavailability of drugs" [21]. A rotating bond is any simple single non-ring bond with a non-terminal atom (except H). So, C-N bonds (amide bond) have a high rotational energy barrier, therefore they are not considered as rotational. The NRotB should not exceed 10. As Table 1 shows, all the studied compounds correspond to this parameter.

Table 1 – Pharmaceutically significant descriptors and drug-like properties

Compound	MW ≤ 500	mi*Log*P ≤ 5	NA ≤ 10	ND ≤ 5	Volume, Å cubed	TPSA, Å squared	NRotB ≤ 10	Rule of 5
1	160.17	-1.20	4	2	146.66	66.76	2	+
2	162.19	-1.01	4	3	152.52	69.92	2	+
3	175.18	-0.75	5	3	158.95	82.28	2	+
4	245.28	0.85	6	2	229.07	88.36	6	+
5	203.24	-1.06	5	3	192.56	82.28	4	+
6	215.29	1.01	4	2	217.90	62.05	5	+
7	235.28	1.27	4	2	222.34	62.05	3	+
8	249.31	1.67	4	2	238.91	62.05	3	+
9	249.31	0.97	4	2	239.15	62.05	4	+
10	345.40	0.66	7	2	316.59	88.99	4	+
11	142.15	-0.09	3	0	128.77	35.54	0	+

NA – number of H bond acceptors; NB – number of H bond donors; TPSA – topological polar surface area; NRotB – number of rotatable bonds

Table 2 – Molinspiration analysis of bioactivity score

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.92	-0.59	-1.34	-0.92	-0.76	-0.38
2	-0.73	-0.35	-0.98	-0.71	-0.68	-0.10
3	-0.55	-0.41	-0.81	-0.73	-0.68	-0.17
4	0.08	-0.41	-0.61	-0.01	-0.38	0.08
5	-0.67	-0.10	-0.86	-0.97	-0.74	-0.14
6	-0.34	0.04	-0.68	-0.61	-0.41	-0.01
7	-0.40	-0.15	-0.44	-0.48	-0.42	-0.06
8	-0.36	-0.15	-0.40	-0.37	-0.38	-0.05
9	-0.19	-0.02	-0.28	-0.45	-0.32	-0.04
10	-0.50	-0.64	-0.52	-0.72	-0.59	-0.26
11	-1.21	-0.72	-1.71	-1.21	-1.05	-0.68

3.2 Prediction of biological activity

Biological activity parameters calculated using Molinspiration Cheminformatics are distributed as follows: more than 0 – significant biological activity; from -0.5 to 0 – moderate activity; less than -0.5 – inactive.

The prediction results are shown in Table 2.

Compound **4** shows significant biological activity as a possible inhibitor of enzymes and a ligand of G-protein coupled receptors. Compound **6** is active as an ion channel modulator. Compound **11** doesn't have any activity against all analyzed parameters.

The biological activity for compounds **1–11** was also predicted using PASS online. The entire obtained data was analyzed and only the highest activity indicators (P_a) of the studied compounds were selected. The results of *in silico* screening are shown in Table 3.

Table 3 – PASS screening results, probability (%)

No	Biological activity	%	No	Biological activity	%
1	CYP2H substrate	92.3	**2**	Sugar-phosphatase inhibitor	91.9
	Sugar-phosphatase inhibitor	87.8		Alkenylglycerophosphocholine hydrolase inhibitor	90.9
	Acrocylindropepsin inhibitor	87.8		UDP-N-acetylglucosamine 4-epimerase inhibitor	88.2
	Chymosin inhibitor	87.8		Glucan 1.4-alpha-maltotriohydrolase inhibitor	87.2
	Saccharopepsin inhibitor	87.8			86.3
	Phobic disorders treatment	87.1		Pullulanase inhibitor	85.8
	Alkenylglycerophosphocholine hydrolase inhibitor	86.9		Ribulose-phosphate 3-epimerase inhibitor	85.3
	Ubiquinol-cytochrome-c reductase inhibitor	85.2		Testosterone 17beta-dehydrogenase ($NADP^+$) inhibitor	85.2
3	Antiischemic, cerebral	86.9	**4**	Saccharopepsin inhibitor	85.8
	Phobic disorders treatment	84.2		Acrocylindropepsin inhibitor	85.8
	Sugar-phosphatase inhibitor=	80.4		Chymosin inhibitor	85.8
				Alkenylglycerophosphocholine hydrolase inhibitor	85.2
				Phobic disorders treatment	84.8
5	Phobic disorders treatment	83.3	**6**	Sugar-phosphatase inhibitor	83.5
	Sugar-phosphatase inhibitor	77.2		Saccharopepsin inhibitor	83.4
	Alkenylglycerophosphocholine hydrolase inhibitor	75.9		Acrocylindropepsin inhibitor	83.4
				Chymosin inhibitor	83.4
7	Saccharopepsin inhibitor	84.3	**8**	Ubiquinol-cytochrome-c reductase inhibitor	79.2
	Chymosin inhibitor	84.3		Alkenylglycerophosphocholine hydrolase inhibitor	78.1
	Acrocylindropepsin inhibitor	84.3		Phobic disorders treatment	77.1
	Phobic disorders treatment	84.2		Sugar-phosphatase inhibitor	75.8
	Sugar-phosphatase inhibitor	82.1			
	Alkenylglycerophosphocholine hydrolase inhibitor	81.7			

Table 3 – PASS screening results, probability (%) (Continued)

No	Biological activity	%	No	Biological activity	%
9	Atherosclerosis treatment	84.7	**10**	Analgesic	86.0
	Potassium channel small-conductance Ca-activated 3 blocker	81.6		Antiinflammatory	84.3
				Antiviral (Picornavirus)	79.4
	Phobic disorders treatment	80.9		Analgesic, non-opioid	78.0
				Insulysin inhibitor	75.7
11	Phobic disorders treatment	92.3		Acrocylindropepsin inhibitor	89.1
	Testosterone 17beta-dehydrogenase (NADP+) inhibitor	89.4		Chymosin inhibitor	89.1
				Aspulvinone dimethylallyltransferase inhibitor	88.4
	Saccharopepsin inhibitor	89.1			

Compounds **1, 2** and **11** show the most significant results. With a probability of 92.3%, compound **1** can exhibit the properties of a CYP2H substrate (CYP2H belongs to the family of heme-containing monooxygenases, metabolizing xenobiotics, including drugs).

Compound **11** shows a high probability of activity (92.3%) in the treatment of phobic disorders. This activity is also found for compounds **1, 3–5** and **7–9**.

The properties of a sugar-phosphatase inhibitor are exhibited by compounds **1–3, 5–8** with a probability from 75.8 (**8**) to 91.9% (**2**). Sugar phosphatase inhibitors are used to treat type 2 diabetes mellitus [22].

Activity in relation to the inhibition of alkenylglycerophosphocholine hydrolase was established for compounds **1**, **2**, **4**, **5**, **7** and **8** (78.1–90.9% of probability). Alkenylglycerophosphocholine hydrolase inhibitors are among "the acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease and other dementias" [23].

Thus, according to the results of PASS prediction, compounds **1–11** are likely to have a wide range of biological activity, including atherosclerosis treatment (**9**), inhibition of the activity of enzymes of peptidase groups (**1**, **3**, **4**, **6**, **7**, **11**), testosterone 17beta-dehydrogenase (NADP+) inhibition (**2**, **11**), anti-ischemic (**3**), analgesic (**10**), anti-inflammatory (**10**) activities and others.

Analyzing the relationship "Structure - Activity" based on the results of screening, we can conclude that the widest set of activities with high P_a was obtained for small molecules, for which there are well-studied analogues in the databases. Such examples are 3,5-substituted tetrahydropyran-4-one **1** and its reduction product **2**, as well as the bicyclization product **11**. When passing to the oximes (**3**–**4**) and imino derivatives of the ketone (**5**–**10**), a decrease in the amount of activities and P_a becomes noticeable. It is possible that imino derivatives are less represented in the PASS database than ketones and their other derivatives. More detailed screening reports are provided in the Supplementary material.

3.3 Prediction of toxicological properties

ProTox-II is a virtual laboratory for predicting some of the toxicological properties associated with chemical structure. Prediction is performed using computer models, trained on real experimental data (*in vitro* or *in vivo*). That allow *in silico* calculation of the acute toxicity class and toxicological activity of a compound based on chemical and structural similarity to toxic compounds.

As the prediction results in Table 4 show, compound **10** belongs to toxicity class 6 (non-toxic). Compounds **1–3, 5, 7, 8** and **11** belong to the class 5 (may be harmful if swallowed) with a probability between 54.3 and 69.3%. Toxicity class 4 includes compounds **6** and **9** (harmful if swallowed). Compound **4** is predicted to be class 3 with a 54.3% probability (toxic if swallowed). The prediction accuracy may depend on the number of compounds of a similar class in the training set of the QSAR model.

Table 4 – ProTox-II prediction of LD_{50} and toxicity class

Compound	Predicted LD_{50}, mg/kg	Predicted Toxicity Class	Average similarity, %	Prediction accuracy, %
1	3730	5	78.48	69.26
2	3000	5	72.06	69.26
3	3000	5	50.79	67.38
4	284	3	47.17	54.26
5	3000	5	41.59	54.26
6	1300	4	43.84	54.26
7	3000	5	46.85	54.26
8	3000	5	50.57	67.38
9	840	4	43.29	54.26
10	5600	6	72.37	69.26
11	3730	5	76.03	69.26

When analyzing the relationship "Structure - Toxicity" in a series of studied derivatives, it can be noted that the elongation of the substituent chain leads to a change in the toxicity class compared to their analogues. For example, the toxicity of compound **4** compared with **3**; or the toxicity of **9** compared

with **7** and **8**. However, to draw a more accurate conclusion, a series with a large number of derivatives is needed, which is beyond the scope of this study.

ProTox-II also predicts several types of toxicity, such as carcinogenicity, mutagenicity, hepatotoxicity, immunotoxicity, cytotoxicity, etc. According to the prediction results, compounds **1–9** are not active for all types of toxicity presented in ProTox-II models. Compounds **10** and **11** might exhibit carcinogenic properties (the probabilities are 53 and 55% relatively).

4. Conclusion

The physicochemical and pharmacokinetic parameters of 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one **1** and its new derivatives **2–11** were determined, *in silico* screening of biological activity and prediction of their toxicity were carried out. Physicochemical and pharmacokinetic parameters were evaluated using the Molinspiration Cheminformatics service. It was found that compounds **1–11** corresponded to Lipinski's rule for drug-like compounds.

As predicted in Molinspiration, compound **4** exhibits significant biological activity as a possible enzyme inhibitor and G-protein coupled receptor ligand. Compound **6** is active as an ion channel modulator.

Virtual PASS screening identified compounds with potential antidiabetic activity (**1–3, 5–8**) and activity in the treatment of phobic disorders and dementias (**1–5**, **7**, **8**, **11**). Compound **1** can potentially act as a substrate for CYP2H, and inhibitors of enzymes of the peptidase group are **1**, **3**, **4**, **6**, **7**, **11**.

As a result of QSAR prediction based on LD_{50} calculated in ProTox-II, compound **10** belongs to class 6; compounds **1–3**, **5** and **8** belong to the 5th class of toxicity; compounds **6** and **9** belong to the 4th class. Compound **4** belongs to class 3. Compounds **1–9** do not exhibit the toxicities shown in the ProTox-II models. Compounds **10** and **11** may be carcinogenic.

The results show that 3,5-bis(hydroxymethyl)tetrahydro-*4H*-pyran-4-one and its new derivatives demonstrate a wide spectrum of activity *in silico* and can be used for the synthesis of potential biologically active compounds.

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