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Hit identification of CK2 inhibitors by methods of virtual screening

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Aim. To search for new CK2 inhibitors by virtual screening. **Methods.** Virtual screening of a small organic compounds library was performed by molecular docking using the Autodock 4.2.6 package and pharmacophore screening with the "PharmDeveloper" program. The compound activity was determined by *in vitro* biochemical tests using γ-P32 ATP. **Results.** 298 compounds were selected for biochemical testing according to the results of virtual screening. *In vitro* experiments showed that 18 compounds have inhibitory activity against CK2 with IC_{50} in the range of 1.4 to 20 μM. The active compounds belonged to 15 chemical classes. **Conclusions.** A number of effective CK2 inhibitors were found using molecular modeling and biochemical testing methods. LE values of these compounds were higher than 0.3 that makes these compounds excellent candidates for further drug development.

K e y w o r d s: CK2 protein kinase, molecular docking, pharmacophore modeling, virtual screening, *in vitro* testing.

Introduction

Casein kinase II, CK2, is a unique protein kinase that phosphorylates serine/threonine as well as the tyrosine amino acid residues. Human CK2 is a tetrameric enzyme composed of two catalytic subunits (CK2α and/or CK2α') and two regulatory subunits of CK2β [1]. CK2 is the most pleiotropic kinase among the protein kinase superfamily [2]. One of the explanations of such a pleiotropy may be that CK2 is present in all compartments of the cell from the nuclear to the plasma membrane, where it can interact with a large number of substrates [3, 4]. Taking into account all these facts, it is not surprisingly that CK2 is involved

in the regulation of the most important processes in the cell and organism: proliferation and survival [5], apoptosis [6], angiogenesis [7], DNA damage and repair [8], ER stress response [9], regulation of the carbohydrate metabolism [10]. Recent studies have reported a critical role of CK2 in embryogenesis and cell differentiation [11].

Additionally, the researchers showed the involvement of CK2 in the development of a number of pathologies, in particular cancer [12], Alzheimer's disease [13], even viral infections [14]. Therefore, CK2 may be a potential therapeutic target [15].

Almost all CK2 inhibitors block the ATP-acceptor site. Benzoimidazoles, anthraquinones, flavonoids, coumarins, and pyrazolotriazines are the most represented families of CK2 inhibitors [16]. Nowadays, only one of them – CX-4945 passed the second stage of clinical trials [17].

The department of Medicinal Chemistry of Institute of Molecular Biology and Genetics NASU is developing, including search, optimization, synthesis and biological evaluation, new inhibitors of CK2 as well as inhibitors of other enzymes for during at least 10 years. Among them, there are many perspective classes, such as 3-carboxy-4(1H)-quinolone derivatives [18], 4,5,6,7-tetrahalogeno-1H-isoindole-1,3(2H)-diones [19], flavone derivatives [20, 21] and (thieno[2,3-d]pyrimidine-4-ylthio)carboxylic acid derivatives [22, 23].

The aim of this work was to search for new CK2 inhibitors using virtual screening (molecular docking and pharmacophore screening) of the collection of the Department of Medicinal Chemistry comprising more than 150,000 compounds.

Materials and methods

Molecular docking

Preparation of ligand and receptor molecules. Autodock 4.2.6 programs package was used for the receptor-based flexible docking [24]. Ligands were prepared by Vega ZZ (command line) [25] and MGL Tools 1.5.6 [24]. The incoming formats of receptor and ligands data were converted into PDBQT-format with Vega ZZ in AUTODOCK force field. This format contains the coordinates of the atoms and partial charges. Hydrogen atoms were removed from nonpolar atoms. The receptor was prepared using MGL Tools and AutoGrid [24].

Table 1. **Docking parameters**

Parameter	Value
Translation step	2 Å
Quaternion step	50°
Torsion step	50°.
Torsional degrees of freedom and coefficient	2 / 0.274
Cluster tolerance	2 Å
External grid energy	1000
Max initial energy	0
Max number of retries	10 000
Number of individuals in population	300
Maximum number of energy evaluations	850 000
Maximum number of generations	27 000
Number of top individuals to survive to next generation	1
Rate of gene mutation	0,02
Rate of crossover	0,8
Mode of crossover	arithmetic
Alpha parameter of Cauchy distribution	0
Beta parameter Cauchy distribution	1
Number of Lamarckian Genetic Algorithm (LGA) runs	50

We have used docking parameters reported earlier [26]. They are shown in table 1.

Flexible docking. The catalytic subunit of protein kinase CK2 complex with a stable analogue of ATP (PDB code 3NSZ) was used as a target for docking [27]. Water molecules, ions, and ligands were removed from the PDB file.

Pharmacophore modeling

Pharmacophore modeling was carried out using "PharmDeveloper" programs (conversion of models and screening collection of compounds to the required formats, pharmacophore screening, rescoring of results) [28] and Discovery Studio Visualizer 4.0 (constructing pharmacophore models) (http://accelrys.com/).

Development of pharmacophore models. Two pharmacophore models were used for pharmacophore screening. These models were constructed based on the model developed in our previous study [28]. It included a donor (R = 1 Å, weight = 11) and an acceptor (R = 0.5 Å, weight = 13) of hydrogen bond, a hydrophobic feature (R = 1 Å, weight = 13) and an aromatic feature with directed vector (R = 1.6 Å, weight = 14). The optimized default scores for pharmacophore features are following: for aromatic features – 2.9, for hydrophobic features – 2.4, for hydrogen bond donors/acceptors – 1.4, aromatic->hydrophobic feature – 1.1. These parameters were calculated during optimization and validation of the model based on a sample of active (IC_{50} less than 200 nM) and inactive CK2 inhibitors and were used for the derived models in this study.

In model 1 the donor was changed to the acceptor and its vector was directed to an amino group of the same amino acid (Val116) to which the donor was directed. In model 2 the hydro-phobic feature was shifted toward the phosphate-binding region for 2.1 Å. In order to increase the accuracy of both models, the excluded volumes were determined on the hydrogen atoms of the amino acid residues of the CK2 ATP-binding site (for all R = 1.2 Å, weight = 1).

Pharmacophore screening and rescoring. The developed pharmacophore models were converted from *.chm format which is used in the Accelrys Discovery Studio Visualizer to *.query format.

The screening library was converted to the special format of "PharmDeveloper" program. 250 conformers were generated for each compound and 100 steps of optimization were performed. Further pharmacophore screening of this base was carried out against both developed models.

The rescoring of results was made automatically during screening. The rescoring function is based on the weights, radii, default scores and comparing the values of the molecular descriptors of the investigated ligands with the parameters of such descriptors of known inhibitors of the studied molecular target. These parameters include the mean deviation and the average value of each descriptor and the special correction coefficients. They were calculated on the basis of the sample of known CK2 inhibitors described above.

After rescoring, the compounds were ranked and the best ones were selected for *in vitro* testing.

Visual analysis

A visual analysis of the results of molecular docking (interaction of compounds with the amino acid residues of CK2 ATP-binding site) and the results of the pharmacophore modeling

Technical details

All calculations were carried out on computer cluster of the Department of Medicinal Chemistry of the Institute of Molecular Biology and Genetics of the NASU. The cluster was built using the BEOWULF technology (see Fig. 1) [29]. The BEOWULF architecture allows scaling power with increasing cluster nodes. The cluster consists of a master node and slave nodes. The master node serves as the center for assigning tasks and the storage location of the cluster file system.

Nowadays, [the] cluster of the Department of biomedical chemistry of the Institute of molecular biology and genetics of the NASU has 24 cores with a frequency of 5.2 GHz.

In vitro testing

Compounds were tested using *in vitro* kinase assay [30]. Each test was done in triplicate in a reaction volume of 30 μL, containing 6 μg of peptide substrate RRRDDDSDDD (New England Biolabs); 10 units of recombinant human CK2 holoenzyme (New England Biolabs);

Fig. 1. Classical scheme of the cluster BEOWULF: 1 – master node; 2 – intracluster distributor; 3 – slave nodes; 4 – internet.

50 μM ATP and γ-labeled ^{32}P ATP, diluted to specific activity of 100 μCi/μM; CK2 buffer (20 mM Tris-HCl, pH 7.5; 50 mM KCl; 10 mM MgCl2) and inhibitor in varying concentrations. Incubation time was 20 min at 30 ºC. The reaction was stopped by adding 10 μL 5 % o-phosphoric acid and the reaction mixture was loaded onto 20-mm discs of phosphocellulose paper (Whatman). Disks were washed three times with 1 % o-phosphoric acid solution, air-dried at room temperature and counted by the Cherenkov method in a beta-counter (LKB). As a negative control an equal volume of DMSO was added to the reaction mixture. The inhibition percent was calculated as a ratio of substrate-incorporated radioactivity in the presence of inhibitor to the radioactivity incorporated in control reactions, i.e. in the absence of inhibitor. Serial dilutions of inhibitor stock solution were used to determine its IC_{50} concentration.

Results and Discussion

Combinatorial library of more than 150,000 organic compounds was used for virtual screening (molecular docking and pharmacophore screening) towards human CK2.

258 compounds for *in vitro* testing were selected using molecular docking and pharmacophore modeling followed by visual exception. According to the results of *in vitro* testing [,] 18 compounds showed inhibitory activity with IC_{50} values in the range from 1.4 to 20 μM. Structures and IC_{50} of the tested compounds are shown in Table 2.

18 compounds are referred to 15 chemical classes of inhibitors. 9 compounds were found using molecular docking and 9 – using pharmacophore screening. 9 compounds (**1a**, **2**, **3**, **8**, **10**, **12**, **13**, **14**, **15**) have IC_{50} less than 5 μM.
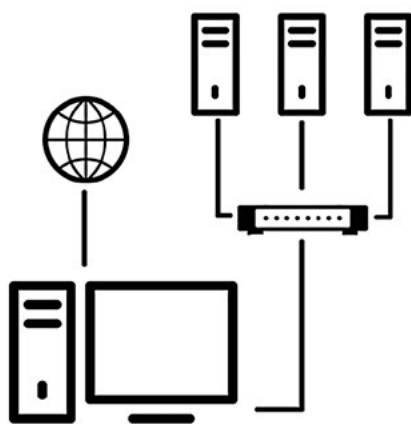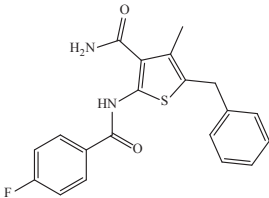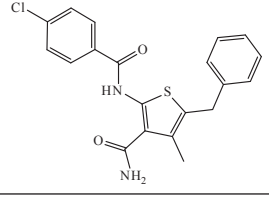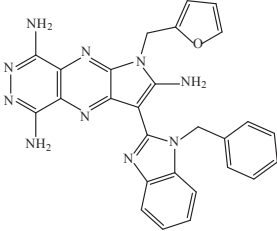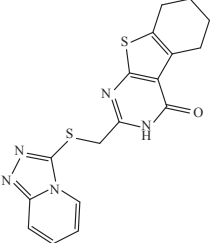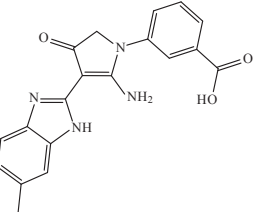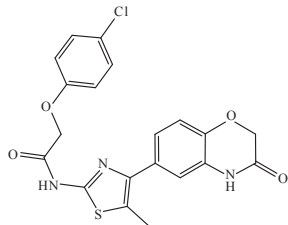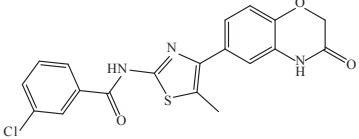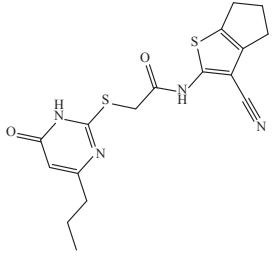
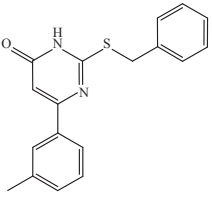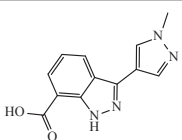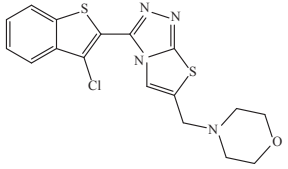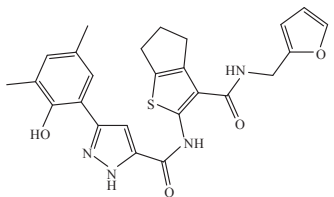9 compounds found during pharmacophore screening were additionally docked into the ATP-binding site of CK2 to study their binding to the kinase active site. The binding modes of these compounds corresponded almost completely to the binding modes which were the
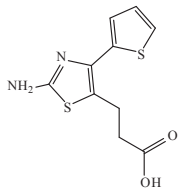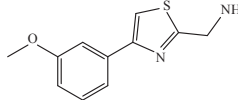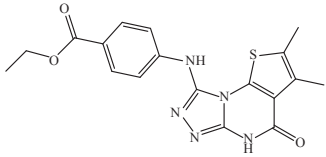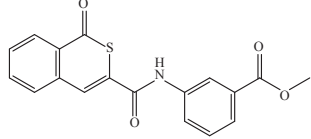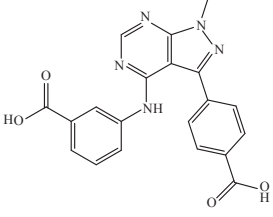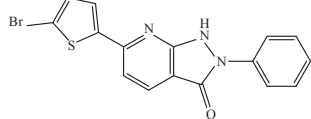
Table 2. **Structure, IC$_{50}$, LE and physicochemical properties of studied compounds**

Scaffold	Compound	Structure	IC$_{50}$, μM	LE*	Heavy atom **	MW	#HD	#HA	#RB	cLogP	cLogS
1	1a		2.5	0.3	26	368	2	2	5	3.9	-6.8
1	1b		7.9	0.27	26	385	2	2	5	4.4	-7.3
2	2		1.4	0.21	38	503	3	8	5	3.8	-7.2
3	3		5	0.29	25	369	1	5	3	3.4	-5.1
4	4		14.4	0.26	26	348	3	6	3	2.7	-3.8

*LE – ligand efficiency. **Heavy atom – number of non-hydrogen atoms.

295

Scaffold	Compound	Structure	IC$_{50}$, μM	LE*	Heavy atom **	MW	#HD	#HA	#RB	cLogP	cLogS
5	5a		6.9	0.24	29	430	2	5	5	3	-5.9
5	5b		12.6	0.25	27	400	2	4	3	3.2	-6
6	6		5.6	0.29	25	374	2	5	6	3.2	-5.5
7	7		15.8	0.3	22	308	1	3	4	4.3	-5.7
8	8		3	0.42	18	315	2	4	2	2.5	-2.2
9	9		20	0.26	25	391	0	4	3	3.6	-5.6
10	10		2	0.26	30	477	4	4	6	4.7	-7.2

Scaffold	Compound	Structure	IC$_{50}$, µM	LE*	Heavy atom **	MW	#HD	#HA	#RB	cLogP	cLogS
11	11а		5.5	0.45	16	254	2	4	4	2	-3.6
11	11б		11	0.45	15	220	1	3	3	1.5	-3.5
12	12		3	0.28	27	383	2	6	5	2.5	-4.9
13	13		2.7	0.32	24	339	1	5	4	2.8	-4.7
14	14		3.7	0.26	29	389	3	8	5	2.8	-5.2
15	15		2.19	0.35	22	372	1	3	2	4.4	-5.5

basis of pharmacophore models. The most active four compounds obtained from pharmacophore modeling are shown in Fig. 2 (mapping with the corresponding pharmacophore models) and in Fig. 3 (docking results).

In Fig. 3 the binding modes of found compounds with the ATP-acceptor site of CK2 are shown. The binding modes were obtained by Autodock 4.2.6. The compounds had typical binding modes of the type I protein kinases inhibitors. All compounds had a hydrogen bond with the amino acid residues of the hinge region (Val116 and/or Glu114). Compound **3** (Fig. 3b) formed a hydrogen bond with the Asp175 in phosphate-binding pocket. Compounds **8** and **13** (Fig. 3 c,e) formed hydrogen bonds with Asn118 and additionally fixed the molecule in the active site. The main

feature of binding modes of all compounds is a large number of hydrophobic interactions with the amino acid residues of the ATP-binding site: Val66. Val53. Phe113. Ile174. Ile95. Met163. π-π interaction with hydrophobic amino acid residue Phe113 also significantly contributed to stabilizing the inhibitor in the CK2 active site.

Notably, the physicochemical properties of the studied inhibitors are in accordance with the Lipinski's rules, which makes the compounds suitable for further research and development of potential drugs. Additionally, parameter LE (ligand efficiency) was used to estimate the contribution of each atom to the compound activity. It is measured in Kcal/mol/number of heavy atoms. LE is also an important indicator of lead-likeness for further optimization studies. Remarkably, several compounds had LE indices greater than 0.3 (see Table 2), which is a widely accepted lower limit, in particular, values 0.3, 0.3, 0.42, 0.45, 0.45, 0.32 were obtained for compounds **1a**, **7**, **8**, **11a**, **11b** and **13**. Therefore, some of these compounds may be agood starting point for the development of new effective and specific CK2 inhibitors.

Conclusions

As a result of virtual screening of the 150,000 small-organic compounds library a series (18 compounds) of CK2 inhibitors were found. IC_{50} of studied inhibitors ranged from 1.4 to 20 μM. These 18 inhibitors belonged to 15 scaffolds. Correspondence of all compounds **to drug-like properties** and high values of LE for compounds **7**. **8**. **11a** and **11b** (0.3. 0.42. 0.45. 0.45 Kcal/mol/number of heavy atoms.
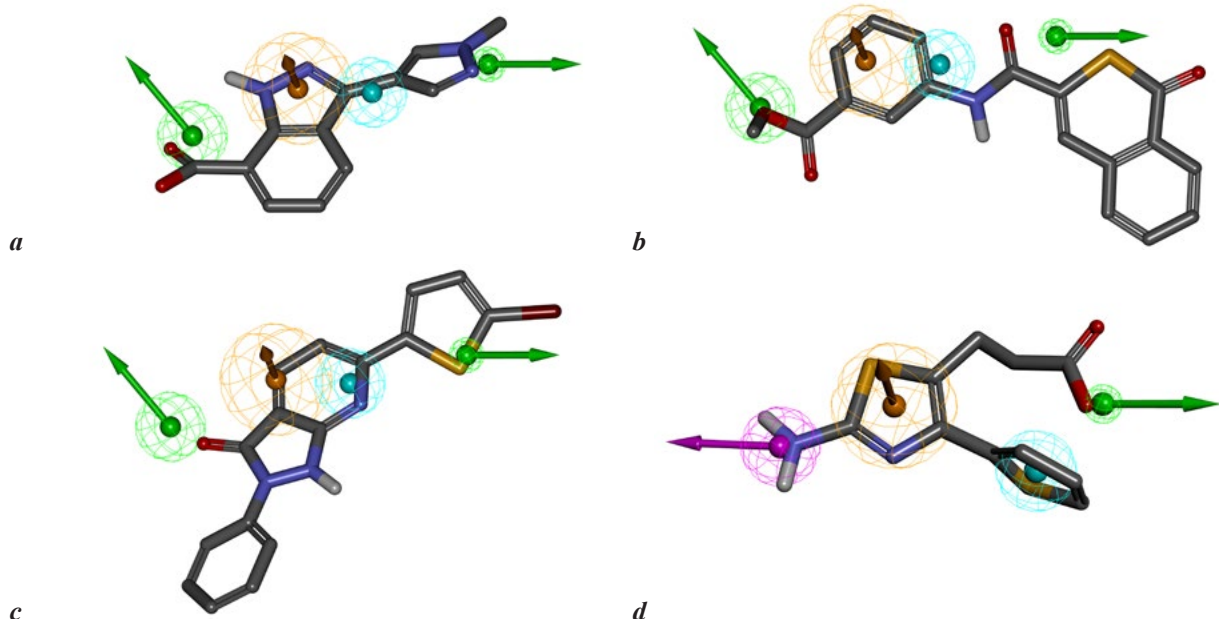

Fig. 2. Mapping compounds **8** (a). **13** (b). **15** (c) to pharmacophore model **1**. compound **11a** (d) to pharmacophore model **2**. Pharmacophore features are labeled with green (H-bond acceptor), purple (H-bond donor), orange (aromatic) and cyan (hydrophobic) colors.
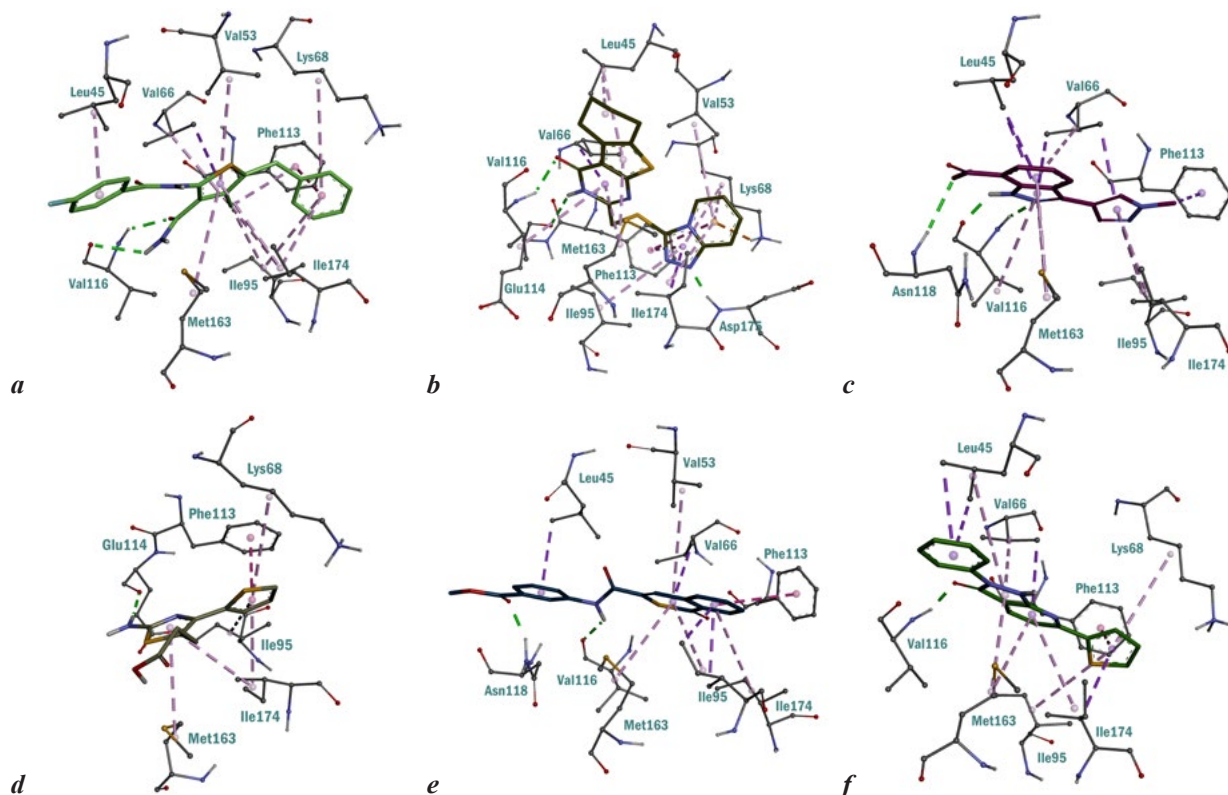
Fig. 3. The complexes of compounds **1** (a). **3** (b). **8** (c). **11a** (d). **13** (e) and **15** (f) with ATP-acceptor site of CK2. H-bonds are shown by green dashed lines, hydrophobic interactions – purple dashed lines.

respectively) make these compounds excellent candidates for further development of effective CK2 inhibitors and potential drugs.

Funding

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Ідентифікація сполук-хітів – інгібіторів CK2 методами віртуального скринінгу.

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Мета. Пошук нових інгібіторів протеїнкінази CK2. **Методи.** Віртуальний скринінг бібліотеки низькомолекулярних сполук проводили методами молекулярного докінгу, програмним пакетом Autodock 4.2.6 та фармакофорного моделювання – програмою «Pharm-Developer». Активність інгібіторів визначали у біохімічних тестах *in vitro* (із використанням γ-P^{32} АТФ). **Результати.** Віртуальним скринінгом було відібрано 298 сполук для біохімічного тестування. Експерименти *in vitro* показали, що 18 сполук проявляють інгібувальну активність щодо CK2 із IC$_{50}$ в межах від 1.4 до 20 μM. Активні сполуки належать до 15 хімічних класів. **Висновки.** За допомогою методів молекулярного моделювання та біохімічного тестування було знайдено ряд інгібіторів CK2, що мали показник LE вище 0.3 та є перспективними для подальшої оптимізації з метою створення лікарських засобів на їхній основі.

К л ю ч о в і с л о в а: протеїнкіназа CK2, молекулярний докінг, фармакофорне моделювання, віртуальний скринінг, *in vitro* тестування.

Идентификация хит-соединений – ингибиторов CK2 методами виртуального скрининга.

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Цель. Поиск новых химических соединений со способностью ингибировать протеинкиназу CK2. **Методы.** Виртуальный скрининг библиотеки низкомолекулярных органических соединений осуществляли при помощи методов молекулярного докинга программным пакетом Autodock 4.2.6 и фармакофорного моделирования – программой «PharmDeveloper». Активность ингибиторов изучали при помощи биохимических тестов *in vitro*, используя γ-P^{32} АТФ). **Результаты.** Виртуальным скринингом было отобрано 298 соединений для биохимического тестирования. Эксперименты *in vitro* показали, что 18 соединений ингибируют протеинкиназу CK2 в диапазоне значений IC$_{50}$ от 1.4 до 20 μM. Активные соединения принадлежат 15 химическим классам. **Выводы.** Используя методы молекулярного моделирования и биохимического тестирования было обнаружено ряд ингибиторов протеинкиназы CK2, со значением LE выше 0.3, которые являются перспективными для последующей оптимизации для разработки на их основе лекарственных средств.

К л ю ч е в ы е с л о в а: протеинкиназа CK2, молекулярный докинг, фармакофорное моделирование, виртуальный скрининг, *in vitro* тестирование.