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HIGH-THROUGHPUT SCREENING OF NEW ANTIMITOTIC COMPOUNDS BASED ON CSLabGrid VIRTUAL ORGANIZATION

Within the framework of CSLabGrid virtual organization, the repository of 3-D models of cytoskeletal proteins (tubulins and FtsZ-proteins) has been created using Grid calculations. The repository of structures of canonical anti-microtubule compounds (inhibitors of tubulin polymerization) as well as library of ligands suitable for high-throughput screening (HTS) in Grid has been developed. Having screened the library, 1,164 compounds that demonstrated an elevated affinity with tubulin molecules: 205 to α-tubulin and 959 to β-tubulin are selected. Among 2,886 compounds synthesized at the Institute of Organic Chemistry of the NAS of Ukraine, 6 ones have been established to be promising inhibitors of α- and β-tubulin polymerization in such human pathogens as Pneumocystis carinii, Giardia intestinalis Ajellomyces capsulatus, Ajellomyces capsulatus, Neosartorya fumigata and Candida albicans. These compounds have been recommended for subsequent experimental evaluation of their biological activity as new pharmacological agents.

Keywords: Grid, virtual organization, structural bioinformatics, cytoskeleton, tubulin, benzimidazole compounds, tubulin depolymerization, antimitotic activity, molecular docking, high-throughput screening, and drugs.

INTRODUCTION. HISTORY OF RESEARCH

Cytoskeleton is a highly dynamic structure of the cell, which is involved in a multitude of processes, including mitosis, meiosis, cytokinesis, support and adaptation of cell shape, exo- and endocytosis, cell movement, active transport, etc. [1, 2]. For being involved in the most fundamental processes of cell vital functions, the proteins and macromolecular complexes that form the cytoskeleton structures (microtubules, microfilaments, and intermediate filaments) are important targets for different classes of natural and synthetic compounds [3]. Due to the ability of α- and β-tubulin molecules (that form microtubule protofilaments) and their bacterial homologs, FtsZ-proteins, to bind in specific way the low molecular compounds of different nature, the microtubules control the response of eukaryotic cells to the action of various chemical factors [4—8]. Some of these compounds are bound to free tubulin monomers (*colchicine, vinblastine*, etc.) and prevent them from polymerization or, vice versa, interact with tubulin polymerized molecules and prevent them from dissociation into monomers (*taxol*) [9, 10]. There are also substances that act similarly on actin filaments stabilizing them (*phalloidin*) or preventing actin monomers from polymerization (*latrunculin*) [11].

Therefore, tubulin and its bacterial homologue, FtsZ protein, actin, bacterial proteins MreB and ParM, proteins and intermediate filaments, and a large group of proteins that directly interact with them or involved in regulation of their structure through various posttranslational modifications are important targets for a wide range of commercially important drugs (*anticancer, fungicidal, herbicidal, antiprotozoal, antihelmintic, and other agents*). In addition, these proteins are essential targets for creating low-molecular agents that can be used as tools in the study of molecular mechanisms of the most important and fundamental processes of birth, life, and death of cells [12—14].

Despite a long history of cytoskeleton research using methods of biochemistry, molecular biology, cell biology, only in the last decade, researchers started to comprehend the basic structural, molecular, and cellular mechanisms of cytoskeleton due to a progress in structural biology and bioinformatics. The latter explains a record-breaking capacity of cytoskeleton structural and biological studies *in silico*. The team of authors hereof launched a systematic study of cytoskeleton structure and functions more than 15 years ago. The success of research was achieved due to the simultaneous use of computational and experimental methods.

From the beginning of the formation of Ukrainian National Grid it has become clear that methodological developments on molecular simulation, identification of ligand binding sites on the surface of the protein molecule, and assessment of stability of these complexes (developed by the team of authors) can be successfully combined with technologies for distributed computing on CPU and GPU, as well as be adapted to Grid calculations [15—18]. Such studies require considerable computing resources at the stages of preparing the targets and compound libraries, screening, molecular docking, and final validation of complexes with promising agents [15, 17]. To solve the computational problems arising in connection with the cytoskeleton study, in 2011, CSLab Grid laboratory, a virtual organization (http://ifbg.org.ua/uk/cslabgrid; http://www.youtube.com/user/ CSLabGrid), was created on the basis of Grid site of the Institute of Food Biotechnology and Genomics (IFBG) of the NAS of Ukraine (http://ifbg.org.ua) [19]. CSLabGrid VO is a voluntary association of professionals using consolidated resources from various geographically differentiated clusters to jointly address scientific and applied problems in the field of molecular and cell biology research of cytoskeleton using both the *in silico* biological tools (structural biology and bioinformatics) and the modern instrumental studies (electron microscopy, confocal microscopy, etc.).

Today, the team of authors has created a repository of 3D models of molecules of the eukaryotic cytoskeleton proteins (tubulin and proteins associated with microtubules) and the prokaryotic homologues of tubulin (FtsZ proteins). These models have been verified by indices of stereochemical correctness, quality of packaging, probability of stacking, and results of molecular dynamics. Respective libraries of anti-microtubule substances belonging to the classes of *benzimidazoles, phosphorothioamides*, *dinitroanilines*, and *taxanes*. The above libraries of targets and ligands can be used in computational experiments performed and planned for the near future as part of joint research within the framework of CSLabGrid virtual organization (Fig. 1, see the color inset).

The most successful example of virtual research and implementation of program principles of CSLabGrid virtual organization is large-scale experiment on search of new compounds with high affinity with α- and β-tubulins of pathogens and pests. As a result of numerous studies, there have been established specific sites where anti-microtubule compounds are bound to molecules of different chemical nature on the surface of α- and β-tubulins. These sites are characterized by an ordered spatial location and a particular topology. It should be noted that representatives of different taxonomic groups of eukaryotes have certain distinctions of primary structure (in terms of amino acid composition) of tubulin molecules, which

define certain structural features of these sites. This fact is the basis for molecular design and screening of compounds with high affinity with the tubulins of pathogenic organism (*protozoa, fungi, worms*, etc.) and low affinity with the human tubulins. This scientific platform was chosen as basis for selecting biologically active compounds from the library of the Institute of Organic Chemistry (IOC) of the NAS of Ukraine using a high-throughput molecular screening technique that involves direct computations in Grid and methods developed by the team of authors for virtual assessment of capacity of the «candidate» compound to interact with tubulin molecules.

The above task required the preparation of libraries of target proteins including the existing spatial models of human tubulin isoforms and tubulin molecules of pathogens, such as representatives of various pathogenic protozoa, fungi (*Microsporum, Epidermophyton, Trichophyton,* etc.), and worms (*Ascaridina, Trichurida, Cestoda, Digenea, Enoplea*, etc.). To solve the problem it was also necessary to revise carefully the existing repository of spatial structures of target proteins from the Protein Data Bank (ftp.wwpdb.org) and to reconstruct the structures of tubulin molecules that at the time of experiment were not presented in the CSLabGrid repository.

The use of Grid applications for this research was fully justified by a need to process large amount of structural and biological information. Thus, in the case of human tubulin, there are 25 tubulin isoforms (10 isoforms of α-tubulin, 11 ones of β-tubulin, 2 isoforms of γ-tubulin, one of δ-tubulin, and one of ε-tubulin), which taking into account the fact that there are, at least, four known binding sites, require considerable computing resources at the stage of preparation of the structures (optimization, molecular dynamics), screening, docking, and molecular dynamics simulation of ligand-protein complexes.

GENERAL TECHNICAL DATA OF GRID CLUSTER OF IFBG OF UKRAINE

At the moment of the project implementation, the grid cluster incorporated:

- 1 server *HP ProLiant* AV340A (2 x *Intel Xeon* E5504 Quad-Core (2.0GHz/4MB), 6 x 2 GB =12 GB DDR3.250 GB + 500 GB + 500 GB = 1.250 TB);
- 1 server: *Supermicro SuperServer* 6027R-TLF (2 x *Intel Xeon* E5-2650 (16 cores, 32 traffics); 2 x 4 Gb DDR3-1333; 4 x 1000 GB SATA);
- 9 servers (Intel Xeon 3.2 GHz, 36 cores, RAM=2 GB x 9 = 18) and 2 disc storages: *Qnap TS-410 Turbo* = 12 TB and *Dell PowerEdge* 1800 = 3 TB.

The bandwidth of external channel for communication with other clusters of the National Grid network is 10 Gb.

SOFTWARE COMPONENT OF CSLabGrid VO

For the operation of CSLabGrid (http://ifbg.org.ua/uk/cslabgrid), respective software has been installed on the computing cluster of IFBG. In particular, this software includes molecular model packages: I-TASSER 2.1 [20] and Modeller 9.11 [21]. For the molecular dynamics calculations Gromacs v.4.5.4; Gromacs v.4.5.5; NAMD v.2.8, and AmberTools-1.5 have been installed; for high-throughput molecular screening UCSF DOCK 6.5 software package is used (http://dock.compbio.ucsf.edu) [22].

Final evaluation of «leaders» among the substances is based on evaluation functions for the results of flexible docking in CCDC GOLD 5.2 program (www.ccdc.cam.ac.uk, local computations), as well as upon the results of molecular dynamics calculations for the selected complexes using Gromacs (Grid computationa). The calibration of system for docking is based on N-(3,5-dimethoxyphenyl)-3-[3-(3-methoxyanilino)-1H-1,2,4-triazole-5-il]pyridine-2-amine (SID 104 060 517, CHEMBL372849) and bovine (*Bos taurus*) α-tubulin model [23].

PREPARATION OF COMPOUND LIBRARY

The IOC and IFBG researchers have collectively created the library of ligands based on a collection of imidazole compounds previously synthesized in IOC. These compounds are avail-

able for further experimental verification. Currently, the library (formats: *.sd, *.mol, *.mol2) has 2886 individual compounds, excluding conformers and stereoisomers (>5000 structures). At the same time, based on the results of PubChem screening, the researchers have prepared a library that, as of today, includes 299,607 compounds (formats: *.sd, *.mol, *.mol2) containing a benzimidazole fragment. Also, 7 000 000 compounds have been obtained from the database of *AKos-Consulting&Solutions Deutschland GmbH* (http://www.akosgmbh.de). So, the resulting library of ligands has numbered 7,302,993 compounds.

To prepare the ligand library and to screen it using UCSF DOCK 6.5, an OpenBabel program was used which made it possible to automatically add hydrogen atoms to heavy atoms and to generate spatial conformation of chemical compounds. The substances which contain reactive groups-substituents (selected based on *pan assay interference compounds* filters compiled upon the research results) were filtered (as Smart records) using Marvin Bean program.

The team of authors hereof selected 170 substances with established anti-α-tubulin effect and 51 substances with anti-β-tubulin effect (*B. Taurus*) [PDB: 4I4T] as reference (control) substances. Information about the substances was obtained from the ChEMBL database (www.ebi.ac.uk/chembl/) that contained data on the 2D-structure of bioactive small molecules. Their properties (logP, molecular weight, search criteria for the selection of ligands according to the Lipinski rules, etc.) have been calculated, and a brief description of biological activity (binding constants, potential pharmacological properties, ADMET-data, etc.) has been given. The data for computations are obtained from research publications and cover a large part of modern drugs.

Specific programs for docking and screening require a specific treatment of established database of compounds and reference substances. The substances were transferred to a 3D-structure library and saved in *.mol2 format with partial charges calculated by the Gasteiger-Huckel method taken into consideration [22], using *Chem Axon* Calculator package module (http://www.chemaxon.com/products/calculator-plugins/) with an option to set *pH* (6.5–7.5) to create different levels of ionization.

PREPARATION OF TUBULIN 3D-MODELS FOR MOLECULAR DOCKING AND SCREENING

3D models for 85 isoforms of α-, β-, γ-, and ε-tubulins of pathogens have been built as part of program for the creation of library of proteins and ligands using the Modeller 9.11 package [21]. Forty structures of them belong to α- and β-tubulins: **α-*tubulins*:** TBA_TRYCR (Q27352) of *Trypanosoma cruzi* (African trypanosomiasis or sleeping sickness pathogen); TBA_TRYBR (P04106) of *Trypanosoma brucei rhodesiense* (African trypanosomiasis pathogen); TBA_TOXGO (P10873) of *Toxoplasma gondii* (toxoplasmosis pathogen); TBA1_NAEGR (P11237) of *Naegleria gruberi* (amoebic meningoencephalitis pathogen); TBA_PLAFK (P14642) of *Plasmodium falciparum* (human malaria pathogen); TBA_PLAYO (P12543) of *Plasmodium yoelii* (mammal malaria pathogen); TBA1_ENTHI (P31017) of *Entamoeba histolytica* (dysentery pathogen); TBA1_PNECA (P53372) of *Pneumocystis carinii* (pneumonia pathogen); TBA_CANAX (P87066) of *Candida albicans* (candidiasis or thrush pathogen); TBA_ENCCU (Q8SRI6) of *Encephalitozoon cuniculi* (microsporidiosis pathogen); TBA_NEOCA (Q71G51) of *Neospora caninum* (neosporosis pathogen); TBA2_EMENI (P24634) of *Emericella nidulan* (conidial stage of *Aspergillus nidulans*) (aspergillosis or moldy mycosis pathogen); TBA_AJECA (P53371) of *Ajellomyces capsulatus* (conidial stage of *Histoplasma capslatum*) (histoplasmosis pathogen); TBA1_CHLRE (P09204) of *Chlamydomonas reinhardtii*; TBA_HAECO (P50719) of *Haemonchus contortus* (nematode, ancylostomatosis pathogen); and TBA_LEPDS (Q8WQ47) of *Lepidoglyphus destructor* (storage mite, itch pathogen).

β-*tubulins*: TBB_TRYCR (P08562) of *Trypanosoma cruzi*; TBB_TRYBR (P04107) of *Trypanosoma brucei rhodesiense*; TBB_TOXGO (P10878)

of *Toxoplasma gondii*; TBB_PLAFA (P14140) of *Plasmodium falciparum*; TBB_PLAFK (P14643) of *Plasmodium falciparum* (isolate K1); TBB_PLAF7 (Q7KQL5) of *Plasmodium falciparum* (isolate 3D7); TBB_PNECA (P24637) of *Pneumocystis carinii*; TBB_CANAX (P10875) of *Candida albicans*; TBB_ENCCU (Q8SS99) of *Encephalitozoon cuniculi* (strain GB-M1); TBB_ENCIN (Q9GSR5) of *Encephalitozoon intestinalis* (microsporidiosis pathogen); TBB2_ECHMU (Q9NFZ6) of *Echinococcus multilocularis*; TBB_GIAIN (P05304) of *Giardia intestinalis* (giardiasis pathogen); TBB_LEIME (P21148) of *Leishmania mexicana* (leishmaniasis pathogen); TBB_BABBO (Q04709) of *Babesia bovis* (babesiosis pathogen); TBB2_EMENI (P10874) of *Emericella nidulans*; TBB_AJECA (P41742) of *Ajellomyces capsulatus*; TBB_ASPFU (Q4WA70) of *Neosartorya fumigata* (strain ATCC MYA-4609/Af293/CBS 101355/FGSC A1100) (conidial stage of *Aspergillus fumigatus*) (aspergillosis or moldy mycosis pathogen); TBB_CHLRE (P04690) of TBB_ENCHE (Q24829) of *Encephalitozoon hellem* (microsporidiosis pathogen); *Chlamydomonas reinhardtii*; TBB1_BRUPA (P18241) of *Brugia pahangi* (nematode, filariasis pathogen); TBB_ONCGI (P41387) із *Onchocerca gibsoni* (nematode, filariasis pathogen); TBB_TRITR (O44388) of *Trichuris trichiura* (annelid, trichuriasis pathogen); TBB3_ECHMU (Q9NFZ5) of *Echinococcus multilocularis* (tapeworm, alveococcosis pathogen); and TBB1_ECHMU (Q9NFZ7) of *Echinococcus multilocularis*.

Crystal structure of B. taurus tubulin molecules was used as framework for constructing 3D tubulin models. The following relaxation of obtained promodels was made by MDM in aqueous environment using Gromacs software package.

The next step was to compare the tubulins with each other. It was necessary because of great similarity of the most important sites of ligand binding by molecules of these proteins rather than because of similarity of conserved proteins. However, the results of the analysis showed overlapping structures of certain chemical compounds capable of inhibiting different tubulins. Using Py Mol (http://www.pymol.org/) software, the optimized structures of different types of tubulin have been aligned spatially, with the clusters identified by similarity of binding sites. Thus, the α-tubulin group formed a cluster of 6 types of target proteins and the β-tubulin group formed 3 clusters of targets. Each standard model had, at least, 5—6 proteins with identical binding site by sequence or by spatial structure.

SCREENING OF COMPOUND LIBRARIES USING UCSF DOCK 6.5 SOFTWARE OF THE IFBG GRID CLUSTER

Virtual screening is a computational procedure that involves an automatic database search and selection of chemical compounds which are expected to have certain properties. To perform virtual screening in CSLabGrid VO, the authors chose an approach based on the use of molecular docking. It allowed them to predict the spatial structure of *ligand-protein* complex and to calculate the energy of ligand protein bonds with appropriate evaluation functions taken into account. Therefore, they used UCSF DOCK 6.5 software package for screening. This choice was made due to the availability of version for Unix and a partially visual interface (Chimea) that was very convenient for further analysis. Unlike many other programs, after preparation of protein molecules, the UCSF DOCK software package calculates protein's surface, with an algorithm for aquatic environment computation (radius 1,4 Å) exploring the protein and building a normal (the line perpendicular to protein's surface) for each point of the surface.

According to the DOCK algorithm, spheres centered in the points of the location of corresponding atoms and in the points of overlapping of these spheres are generated, at the next stage. Based on the location of ligand or in the absence of inhibitor, the site is automatically filled with spheres of different diameters in order to cover the space as tightly as possible. The size of the spheres corresponds to the van der Waals radii of the key elements. For convenience, the spheres are represented by clusters based on their size, which allows the researchers to group them and

to identify the location of inhibitor. Based on these data, a grid is built. This grid is an energy map of binding sites for each point of which the respective electrostatic energy and van der Waals energy are computed.

For the final design of experiment in Grid, a receptor hydrogen atoms on all heavy atoms was used, which allowed the researchers to estimate the energy of interaction based on their equation, namely, on a evaluation function of protein-ligand interaction energy, the «grid score» (E_{Grid}):

$$E_{Grid} = E_{vdW} + E_{es},$$

where E_{Grid} is «grid score» of interaction energy; E_{vdW} is energy of van der Waals interaction; and E_{es} is energy of electrostatic interaction.

Generally, E_{Grid} function acts like an evaluation function of molecular mechanical energy, but takes into account only the enthalpy component (i.e., complex interaction with aqueous environment). Following the calculation of «grid score», the program automatically finds in the ligand structure the most rigid and immobile part, and this anchor is fixed in the most energetically favorable position of the molecule, with the remaining radicals selected with respect to the anchor fragment by a stepwise analysis of each position. After this, the rigid fragment is moved to a different position, and this analysis is repeated 200 times. The ligand atoms overlapping the spheres and the results of calculation of interaction make it possible to assess the ligand affinity with target proteins. The analysis of arrangement of hydrogen bonds helps to identify the key remains and to prepare final maps for UCSF DOCK algorithm of molecular screening.

Having virtually screened the total libraries of ligands, 1 164 «leader» compounds that potentially are able to block the tubulin polymerization are selected: 205 for α-tubulin and 959 for β-tubulin.

MOLECULAR DOCKING USING A GENETIC ALGORITHM OF CCDC GOLD PROGRAM

Having analyzed the molecular screening results the researchers selected 50 «leaders» that in terms of «grid score» potentially could inhibit the tubulins of both types (α and β). The next stage of molecular docking was performed on local computer using genetic algorithm of CCDC Gold program. The use of this algorithm enabled a final selection of the most promising compounds based on calculation of binding energy parameters, presence and number of hydrogen bonds. To control the docking, a crystallographic model of *B. taurus* α-tubulin structure was used. The system was calibrated based on a model reference substance N-(3,5-dimethoxyphenyl)-3-[3-(3-methoxyanilino)-1H-1,2,4-triazole-5-il]pyridine-2-amine that was proved to be able to inhibit *B. taurus* tubulin polymerization by 80% [23] (Fig. 2, see the color inset). For completing the docking protocol, complexes with two other inhibitors were built: podophyllotoxin (CHEMBL61-(5R, 5aR,8aR,9R)-5-hydroxy-9-(3,4,5-trimethoxyphenyl)-5a,6,8a,9-tetrahydro-5H-[2]benzofuro[5, 6-f][1,3]benzodioxole-8-on) and CHEMBL409088 ([2-(3-hydroxy-4-methoxyphenyl)-6-methoxy-1-benzofuran-3-il]-(3,4,5-trimethoxyphenyl)methanone). These substances have experimentally proven affinity with GTP-exchange site of tubulin and inhibit its activity by 84 and 80%, respectively (Fig. 3, see the color inset).

The calculation using the genetic algorithm is made through the creation of «populations», i.e. the number of randomly generated conformations mating to each other. If new conformation is preferred, it remains in the gene pool and is involved in new mating. To divide the results obtained by groups, the islands are used. As a result of docking control of reference compounds, the following docking parameters have been established: population size 100, 1.1 for the sample; 10 islands, 100 000 genetic operations. The VDW (van der Waals) and hydrogen bond radii were established to be 4.0 and 2.5 Å, respectively. The most promising conformations were selected on the basis of *Gold Score* evaluation criteria. *Chem Score* and *ASP* parameters were taken into account to improve the search quality and performance. A search radius within the binding site was equal to 9 Å and was set in accordance with

the CCDC recommendation. The same protocol was used for subsequent docking control of compounds and 50 «leader» substances based on the models of pathogen tubulin molecules and a reference structure of *B. taurus* α-tubulin.

Having compared the docking results, 10 ligands were identified to have potential anti-α-tubulin effect and 7 ligands to have anti-β-tubulin effect. Particular attention should be paid to 6 substances that upon the results of Grid virtual screening (UCSF DOCK 6) and docking in CCDC Gold showed a significant affinity with α- and β-tubulin of *Ajellomyces capsulatus, Pneumocystis carinii, Neosartorya fumigata, Candida albicans,* and *Giardia intestinalis* (Fig. 4, see the color inset):

4-[(5-methanesulfonyl-2-nitrophenyl) amino] butanoate (*A. capsulatus* (α-tubulin));

1-phenyl-2-(1H-1,2,4-triazole-3-ilsulfanil) ethane-1-one (*C. trachomatis* (α-tubulin));

4-chloro-3-[(2-hydroxyethyl) (methyl) sulfamoil] benzoate (*P. carinii* (α-tubulin));

3-{[4-(4-chlorophenyl)-5-(pyridine-3-il)-4H-1,2,4-triazole-3-il]sulfonyl}propanoate (*N. fumigata* (β-tubulin));

2-{[2-(4-methoxyphenyl) -2-oxoethyl] sulfonyl} benzoate (C. albicans (β-tubulin)); and

5-[(furan-2-il-methyl) sulfamoil]-2-methoxybenzoate (*G. intestinalis* (β-tubulin)).

The above substances are included in a group of compounds synthesized by IOC of the NAS of Ukraine and currently are verified in *in vitro* experiments as inhibitors of microtubule (tubulin) polymerization for the further study of their possible use as potential drugs to treat infectious and parasitic diseases.

CONCLUSIONS

As a result of high-throughput molecular screening in Grid 1 164 compounds were selected from the library numbering 7,302,993 compounds. The selected compounds have affinity with tubulin molecules of different origin: 205 substances with a-tubulin and 959 compounds with β-tubulin. In addition, 6 «leader» substances (that according to the results of molecular docking and screening have a significant affinity with relevant binding sites on the surface of α- and β-tubulin molecules of *Ajellomyces capsulatus, Chlamydia trachomatis, Pneumocystis carinii, Neosartorya fumigata, Candida albicans*, and *Giardia intestinalis*) have been selected out of 2986 compounds provided by the IOC, which now are available for experimental verification as promising inhibitors of tubulin polymerization.

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ВИСОКОПРОПУСКНИЙ СКРИНІНГ РЕЧОВИН З АНТИМІТОТИЧНОЮ АКТИВНІСТЮ НА БАЗІ ВІРТУАЛЬНОЇ ОРГАНІЗАЦІЇ CSLabGrid

Описано створення репозиторію 3-D моделей білків цитоскелету (тубулінів і FtsZ-білків) у рамках віртуальної організації CSLabGrid з використанням обчислень в Ґрід. Розглянуто питання створення репозиторію просторових структур канонічних антимікротрубочкових агентів (інгібіторів полімеризації тубуліну), а також бібліотеки речовин, придатних для віртуального молекулярного скринінгу в Ґрід. За результатами високопропускного віртуального скринінгу цієї бібліотеки відібрано 1164 речовини з підвищеною спорідненістю до тубуліну: 205 — до α-тубуліну і 959 — до β-тубуліну. Встановлено, що з 2 886 сполук, синтезованих в Інституті органічної хімії НАН України, 6 речовин є перспективними інгібіторами полімеризації α- і β-тубуліну з таких збудників хвороб людини, як *Pneumocystis carinii, Giardia intestinalis, Ajellomyces capsulatus, Ajellomyces capsulatus, Neosartorya fumigata, Candida albicans.* Відповідно ці речовини рекомендовані для подальшої експериментальної оцінки їх біологічної активності з метою застосування як нових фармакологічних засобів.

Ключові слова: Ґрід, віртуальна організація, структурна біоінформатика, цитоскелет, тубулін, бензімідазольні сполуки, деполімеризація тубуліну, антимітотична активність, молекулярний докінг, високопропускний скринінг, фармакологічні засоби.

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ВЫСОКОПРОПУСКНОЙ СКРИНИНГ ВЕЩЕСТВ С АНТИМИТОТИЧЕСКОЙ АКТИВНОСТЬЮ НА БАЗЕ ВИРТУАЛЬНОЙ ОРГАНИЗАЦИИ CSLabGrid

Описано создание репозитория 3-D моделей белков цитоскелета (тубулинов и FtsZ-белков) в рамках виртуальной организации CSLabGrid с использованием вычислений в Грид. Рассмотрен вопрос создания репозитория пространственных структур канонических антимикротрубочковых агентов (ингибиторов полимеризации тубулина), а также библиотеки веществ, пригодных для виртуального молекулярного скрининга в Грид. В соответствии с результатами высокопропускного виртуального скрининга этой библиотеки отобрано 1164 вещества с повышенным сродством к тубулину: 205 – к α-тубулину и 959 – к β-тубулину. Установлено, что из 2 886 соединений, синтезированных в Институте органической химии НАН Украины, 6 веществ являются перспективными ингибиторами полимеризации α- и β-тубулина из таких возбудителей болезней человека, как *Pneumocystis carinii, Giardia intestinalis, Ajellomyces capsulatus, Ajellomyces capsulatus, Neosartorya fumigata, Candida albicans.* Соответственно, эти вещества рекомендованы для дальнейшей экспериментальной оценки их биологической активности с целью использования в качестве новых фармакологических средств.

Ключевые слова: Грид, виртуальная организация, структурная биоинформатика, цитоскелет, тубулин, бензимидазольные соединения, деполимеризация тубулина, антимитотческая активность, молекулярный докинг, высокопропускной скрининг, фармакологические средства.

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