Biomeditsinskaya Khimiya

ISSN 2310-6905 (online), ISSN 2310-6972 (print)

2019 volume 65 issue 2

1. Savosina P.I., Stolbov L.A., Druzhilovskiy D.S., Filimonov D.A., Nicklaus M.C., Poroikov V.V.

Discovering new antiretroviral compounds in Â«Big DataÂ» chemical space of the SAVI library.

Despite significant advances in the application of highly active antiretroviral therapy, the development of new drugs for the treatment of HIV infection remains an important task because the existing drugs do not provide a complete cure, cause serious side effects and lead to the emergence of resistance. In 2015, a consortium of American and European scientists and specialists launched a project to create the SAVI (Synthetically Accessible Virtual Inventory) library. Its 2016 version of over 283 million structures of new easily synthesizable organic molecules, each annotated with a proposed synthetic route, were generated in silico for the purpose of searching for safer and more potent pharmacological substances. We have developed an algorithm for comparing large chemical databases (DB) based on the representation of structural formulas in SMILES codes, and evaluated the possibility of detecting new antiretroviral compounds in the SAVI database. After analyzing the intersection of SAVI with 97 million structures of the PubChem database, we found that only a small part of the SAVI (~0.015%) is represented in PubChem, which indicates a significant novelty of this virtual library. However, among those structures, 632 compounds tested for anti-HIV activity were detected, 41 of which had the desired activity. Thus, our studies for the first time demonstrated that SAVI is a promising source for the search for new anti-HIV compounds.

DOI: 10.18097/PBMC20196502073

2. Sulimov A.V., Kutov D.K., Ilin I.S., Sulimov V.B.

Docking with combined use of a force field and a quantum-chemical method.

The paper presents the results concerning the application of docking programs FLM to combined use of the MMFF94 force field and the semiempirical quantum-chemical method PM7 in the docking procedure. At the first step of this procedure a fairly wide range of low-energy minima of the protein-ligand complex is found in the frame of the MMFF94 force field using the FLM program. The energies of all these minima are recalculated using the PM7 method and the COSMO solvent continuum model at the second step. On the basis of these calculations the deepest minimum of the protein-ligand energy, calculated by the PM7 method with COSMO solvent, is determined, which gives the position of the ligand closest to its position in the crystal of the protein-ligand complex. It is shown that the first step of the combined procedure is performed more quickly and more efficiently in vacuum, rather than with a solvent model.

DOI: 10.18097/PBMC20196502080

3. Zefirov N.A., Lavrushkina E.A., Kuznetsov S.A., Zefirova O.N.

Podophyllotoxin analogue with bicyclo[3.2.1]octane moiety annelated with indole: synthesis, molecular modeling, and biological testing.

C4-Ester derivatives of the anticancer agent podophyllotoxin with bridged moieties can either inhibit polymerization of alpha,beta-tubulin with the formation of microtubules (analogously to the parent molecule) or cause an unusual effect of â€œcurling and shorteningâ€• of the microtubules (MT). In order to predict the effect of bridged podophyllotoxin derivatives on the MT network using computer molecular modeling it is desirable to enhance the structural diversity of their bridged substituents. In the present work we synthesized novel podophyllotoxin ester with bicyclo[3.2.1]octane moiety annelated with indole core. The target compound was obtained by Steglich esterification of podophyllotoxin by rac-exo-(indolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6-carboxylic acid as diastereomeric (6RS,8SR,9RS) mixture, which could not be separated by thin layer or preparative column chromatography on silica gel. Results of biotesting of 4-O-{(6R,8S,9R)-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepto[b]indol-8-ylcarbonyl}-Lpodophyllotoxin on the carcinoma A549 cells proved its ability to cause full depolymerization of microtubules without curling effect at a concentration 10 Î¼M. Cytotoxicity value of the compound estimated in MTT test was in a high nanomolar concentration interval (EC50=710Â±30 nM). Computer molecular docking of both isomers of novel compound and earlier synthesized podophyllotoxin esters with bridged moieties into the 3D model of the colchicine domain in alpha,beta-tubulin revealed the difference in positions of the bridge moieties of new compound and MT-curling ligands and allowed to hypothesize that the atypical action on MT might be caused by positioning of their bridge groups near the GTP binding site in alpha-tubulin.

DOI: 10.18097/PBMC20196502086

4. Vassiliev P.M., Spasov A.A., Yanaliyeva L.R., Kochetkov A.N., Vorfolomeyeva V.V., Klochkov V.G., Appazova D.T.

Neural network modeling of multitarget RAGE inhibitory activity.

Based on the methodology of artificial neural networks, models describing the dependence of the level of RAGE inhibitory activity on the affinity of compounds for target proteins of the RAGE-NF-kB signal pathway have been costructed. A validated database of the structures and activity levels of 183 known compounds, which were tested for RAGE inhibitory activity was formed. The analysis of the AGE-RAGE signaling pathways was carried out, 14 key RAGE-NF-kB signal pathway nodes were found, for which 34 relevant target proteins were identified. A database of 66 valid 3D models of 22 target proteins of the RAGE-NF-kB signal chain was compiled. Ensemble molecular docking of 3D models of 183 known RAGE inhibitors into sites of 66 valid 3D models of 22 relevant RAGE target proteins was performed and minimum docking energies for each compound were determined for each target. According to the method of artificial multilayer perceptron neural networks, classification models were constructed to predict level of RAGE inhibitory activity based on the calculated affinity of compounds for significant target proteins of the RAGE-NF-kB signaling chain. The prognostic ability of these models of RAGE-inhibitory activity was evaluated, the maximum accuracy according to ROC-analysis was 90% for a high level of activity. The

sensitivity analysis of the developed multitarget models were carried out, the most significant targets of the RAGE-NF-kB signal transmission chain were determined. It was found that for high level of RAGE inhibitory activity, the most significant biotargets are not AGE receptors, but eight signaling kinases of the RAGE-NF-kB pathway and transcription factor NF-kB1. Thus, it is suggested that known compounds with high RAGE-inhibitory activity are preferential inhibitors of signal kinases.
DOI: 10.18097/PBMC20196502091

5. Butina Yu.V., Kudayarova T.V., Danilova E.A., Islyaikin M.K.

The prediction of the spectrum of biological activity and antimicrobial properties of diaminoazoles.

The work is devoted to predicting and studying biological properties of N-substituted analogs of 3,5-diamino-1,2,4-thiadiazole, which, in their turn, include in the composition of many drugs that exhibit a wide range of pharmacological actions. For searching of new alternative drugs with an antibacterial activity, but lacking resistance of microorganism strains to them, a computer screening of 2N-alkyl-substituted 5-amino-3-imino-1,2,4-thiadiazolines previously synthesized by us was carried out. The prediction of the spectrum of biological activity, as well as the determination of the probable toxicity of these compounds, was performed using the freely available computer programs PASS, Anti-Bac-Pred, and GUSAR. The study of the antibacterial activity in vitro against gram-positive (Staphylococcus aureus, Staphylococcus saprophyticus, Staphylococcus epidermidis) and gram-negative (Escherichia coli, Pseudomonas aeruginosae) bacterial strains was performed by the disco-diffusion method. Experimental data roughly correspond to the predictions.
DOI: 10.18097/PBMC20196502099

6. Martynova Yu.Z., Khairullina V.R., Gimadieva A.R., Mustafin A.G.

QSAR-modeling of desoxyuridine triphosphatase inhibitors in a series of some derivatives of uracil.

Due to the widespread prevalence, deoxyuridine triphosphatase (UTPase) is considered by modern biochemists and physicians as a promising target for the development of drugs with a wide range of activities. The therapeutic effect of these drugs will be due to suppression of DNA biosynthesis in various viruses, bacteria and protozoa. In order to rationalize the search for new dUTPase inhibitors, domestic and foreign researchers are actively using the QSAR methodology at the selection stage of hit compounds. However, the practical application of this methodology is impossible without existence of valid QSAR models. With the use of the GUSAR 2013 program, a quantitative analysis of the relationship between the structure and efficacy of 135 dUTPase inhibitors based on uracil derivatives was performed in the IC50 range of 30Â¸185000 nmol/L. Six statistically significant valid consensus models, characterized by high descriptive ability and moderate prognostic ability on the structures of training and test samples, are constructed. To build valid QSAR models for dUTPase inhibitors can use QNA or MNA descriptors and their combinations in a consensus approach.
DOI: 10.18097/PBMC20196502103

7. Rudik A.V., Dmitriev A.V., Lagunin A.A., Ivanov S.M., Filimonov D.A., Poroikov V.V.

Xenobiotic toxicity prediction combined with xenobiotic metabolism prediction in the human body.

The majority of xenobiotics undergo a number of chemical reactions known as biotransformation in human body. The biological activity, toxicity, and other properties of the metabolites may significantly differ from those of the parent compound. Not only xenobiotic itself and its final metabolites produced in large quantities, but the intermediate and final metabolites that are formed in trace quantities, can cause undesirable effects. We have developed a freely available web resource MetaTox (http://www.way2drug.com/mg/) for integral assessment of xenobiotics toxicity taking into account their metabolism in the humans. The generation of the metabolite structures is based on the reaction fragments. The estimates of the probability of the reaction of a certain class and the probability of site of biotransformation are used at the generation of the xenobiotic metabolism pathways. The web resource MetaTox allows researchers to assess the metabolism of compounds in the humans and to obtain assessment of their acute, chronic toxicity, and adverse effects.
DOI: 10.18097/PBMC20196502114

8. Tinkov O.V., Grigorev V.Yu., Polishchuk P.G., Yarkov A.V., Raevsky O.A.

QSAR investigation of acute toxicity of organic compounds during oral administration to mice.

The effect of the structure of organic compounds on the acute toxicity upon oral injection in mice was studied using 2D simplex representation of the molecular structure and Random forest (RF) methods. Satisfactory quantitative structure-activity relationship (QSAR) models were constructed (R2 test = 0,61â€“0,62). The interpretation of the obtained QSAR models was carried out. The contributions of known toxicophores with established mechanisms of action were calculated in order to confirm the ability of the interpretation approach to correctly rank them relative to other structural fragments. The influence of the molecular surroundings of some toxicophores was analyzed. We analyzed the contributions of other highly ranked fragments from the list of common functional groups and ring systems in order to find new potential toxicophores. The on-line version of the expert system â€œOCHEMâ€• (https://ochem.eu) and Arithmetic Mean Toxicity (AMT) approach were used for a comparative QSAR study.
DOI: 10.18097/PBMC20196502123

9. Bolshchikov B.D., Tsvetkov V.B., Alikhanova O.L., Serbin A.V.

Modeling and theoretical analysis of ring specific mimicry in view of isomerism within medicinal promising oligomers of "DIVEMA".

The furan or pyran related hetero cycles play basic role in structural units of nucleic acids (NA) and polysaccharides (PS), significantly predetermining their functional specifics. Some of such properties, in great relevancy for medicine, can be imitated through mimicry of polymers synthetic. Particularly, a formation of similar cycloisomeric chains is possible in process of free-radical cyclocopolymerization of divinyl ether (DVE) and maleic anhydride (MA). The products yielded (DVEMA) of general formula [DVE(MA)-alt-MA]n become precursors for a broad family of water-soluble derivatives capable of wide spectrum of bioactivity, including induction of interferon, immune-stimulated and direct antiviral protection. In this connection, the knowledge: what is content of different heterocyclic isomers in backbone of the preparations and what their partial contributions in promotion of the certain

bioactivities observed, are in great importance. Available experimental data (NMR, IR, etc.), controversial for interpretations, didn't elucidate a required estimation of the DVEMA isomerism. The current work represents an independent exploration of the problem via quantum chemistry-based analysis of kinetic (activation barriers) and thermodynamic (enthalpies) priorities in competition between variable isomerism within the chain synthesis. The system is considered in maximal range of hypothetically allowable variations of two levels for double regioselective bifurcations: there are four competitive ways, each of which involves a sequence of four type elementary reactions for a diverse-isomeric formation of chain units. A genesis of six chiral centers (62 stereoisomers permitted) per every of the four part ways was accounted in view for up to 256 isomeric variations in total. The required time-minimized but precisely accurate computations were conducted via B3LYP/6-31G(d), M06-2X/6-311+G(d), M06-2X/6-31+G(2df,p) techniques, which were preselected through model test-systems. As a result, the mechanisms, crucial points and factors for the process-permitted regulation of isomeric content of DVEMA were studied in details. The narrow enough set of most probable enantiomers within highly competitive 5-exo- and 6-endo-ring closing sub-ways was revealed. The results obtained are very actual for an adequate modeling (docking / molecular dynamics) of DVEMA derivatives in their interactions with biopolymer targets, in search for purposed advancement of current background in design and synthesis of highly effective agents for combined antiviral protection (against HIV, flu, herpes, and other infections).
DOI: 10.18097/PBMC20196502133

10. Terekhov R.P., Selivanova I.A., Zhevlakova A.K., Porozov Yu.B., Dzuban A.V.

Analysis of dihydroquercetin physical modification via in vitro and in silico methods.

Flavonoid-mediated materials are promising substances for the design of new functional materials because of their bioactivity, eco-friendliness, and cost-effectiveness. Dihydroquercetin (DHQ) is the major flavonoid in the wood of Larix dahurica Turcz. Previously some new modifications were created on the basis of DHQ, they were characterized by different morphological, physico-chemical and biopharmaceutical properties. This study was performed to research the influence of the solvent on the formation of the solid phase in DHQ microtubes and crystal form as commercially available active pharmaceutical ingredient (API). The choice of the models for the computational simulation was based on the data of differential scanning calorimetry. All calculations were performed using Materials Science Suite. In silico analysis demonstrated that the molecules of solvent are a key player in the formation of the solid phase of the flavonoid-mediated material. Also the comparative analysis of physical characteristics between DHQ microtubes and crystal form was performed. These data give an opportunity to suggest, that DHQ microtubes may have a grate application as the dressing material and in the drug delivering. The results of this study could be helpful for the design of the new flavonoid-mediated materials by crystal engineering.
DOI: 10.18097/PBMC20196502152