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In silico alternatives to animal testing: state of the art

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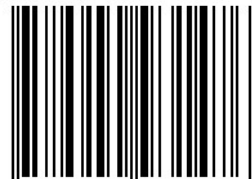
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PSP-39

IN SILICO ALTERNATIVE EKSPERIMENTIMA NA ŽIVOTINJAMA: DOSADAŠNJA SAZNANJA I PERSPEKTIVE**Nebojša Pavlović¹, Svetlana Goločorbin-Kon¹, Karmen Stankov², Maja Đanić³, Bojan Stanimirov², Mladena Lalić-Popović¹, Momir Mikov³**¹ *Univerzitet u Novom Sadu, Medicinski fakultet, Katedra za farmaciju, Novi Sad, Srbija*² *Univerzitet u Novom Sadu, Medicinski fakultet, Katedra za biohemiju, Novi Sad, Srbija*³ *Univerzitet u Novom Sadu, Medicinski fakultet, Katedra za farmakologiju, toksikologiju i kliničku farmakologiju, Novi Sad, Srbija*

In silico metode se danas sve intenzivnije koriste u procesu razvoja novih lekova. Značajne tehnološke inovacije su dovele do razvoja potpuno automatizovanih procesa kontrolisanih mikroprocesorima, koji se označavaju kao skrining velikog broja jedinjenja. Osnovni cilj ovih procesa jeste da se od velikog broja jedinjenja izaberu ona koja imaju najviše šanse da se pokažu kao efikasna u kasnijim fazama razvoja lekova. Većina in silico metoda je bazirana na pretpostavci da strukturno slična hemijska jedinjenja imaju sličnu aktivnost, što ovim metodama daje prediktivni karakter. Brojne softverske tehnike koje su razvijene u cilju olakšavanja procesa razvoja lekova se mogu podeliti na tehnike zasnovane na matematičkom izračunavanju molekulskih osobina samih jedinjenja i tehnike zasnovane na proučavanju interakcija između jedinjenja i njihovih ciljnih proteina. Ove dve glavne kategorije in silico predviđanja biološke aktivnosti se označavaju kao ispitivanja kvantitativnog odnosa strukture i aktivnosti (QSAR) i kao docking studije. In silico metode se danas koriste za predikciju fizičko-hemijskih osobina supstanci, farmakokinetike/ toksikokinetike, delovanja (farmakodinamike) i toksičnih efekata. Primena ovih metoda u procesu razvoja lekova u velikoj meri ubrzava taj proces i smanjuje troškove ispitivanja. Osim toga, smanjuje se i broj životinja uključenih u eksperimentalna istraživanja, što je u skladu sa preporukama regulatornih tela EU i SAD. Najznačajniji primeri lekova koji su dizajnirani primenom kompjuterskih tehnika su inhibitori HIV proteaze nelfinavir i amprenavir. Iako su se in silico metode pokazale kao veoma uspešne na brojnim primerima, one ipak imaju i nedostatke, prevashodno nedostatak standardizacije. Ove metode moraju da se sprovode prema tačno utvrđenim procedurama, baš kao i biološka pretklinička ispitivanja ili kliničke studije, i neophodno je definisati način validacije ovih testova. In silico modeli se neprestano usavršavaju i vremenom će zauzeti još značajnije mesto u procesu razvoja lekova. Zahvalnost: Ovaj rad je podržan od strane projekta AP Vojvodine broj 114-451-2072-/2016 i Horizon 2020 MEDLEM projekta broj 690876.

Ključne reči: in silico, razvoj lekova, QSAR, predikcija

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In silico methods are widely used in the development of novel drugs. Recent technological innovations led to the development of fully automated processes controlled by microprocessors, which are referred as high-throughput screening. The main objective of these processes is to select from a large number of compounds those that are most likely to be effective in the later stages of drug development. Most in silico methods are based on the assumption that structurally similar chemical compounds have similar activity, and therefore these methods have a predictive character. Numerous software techniques that have been developed in order to facilitate the process of drug development can be divided into techniques based on mathematical calculation of molecular properties of compounds and techniques based on the study of interactions between compounds and target proteins. These two main categories of in silico predictions of biological activity are referred to as quantitative structure-activity relationship studies (QSAR) and as docking studies. In silico methods are now being used to predict the physico-chemical properties of substances, pharmacokinetics, pharmacological effects and toxic effects. The application of these methods in drug development greatly speeds up the process and reduces the costs of testing. In addition, it leads to reduction of the number of animals included in the experimental study, which complies with EU regulation. The most important examples of drugs designed using computer techniques are HIV protease inhibitors nelfinavir and amprenavir. In silico methods also have drawbacks. These methods have to be implemented according to established procedures, as well as the biological preclinical tests or clinical trials. In silico models are continuously being improved and it is obvious that with time they will have more prominent role in the drug development.

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Key words: in silico, drug development, QSAR, prediction