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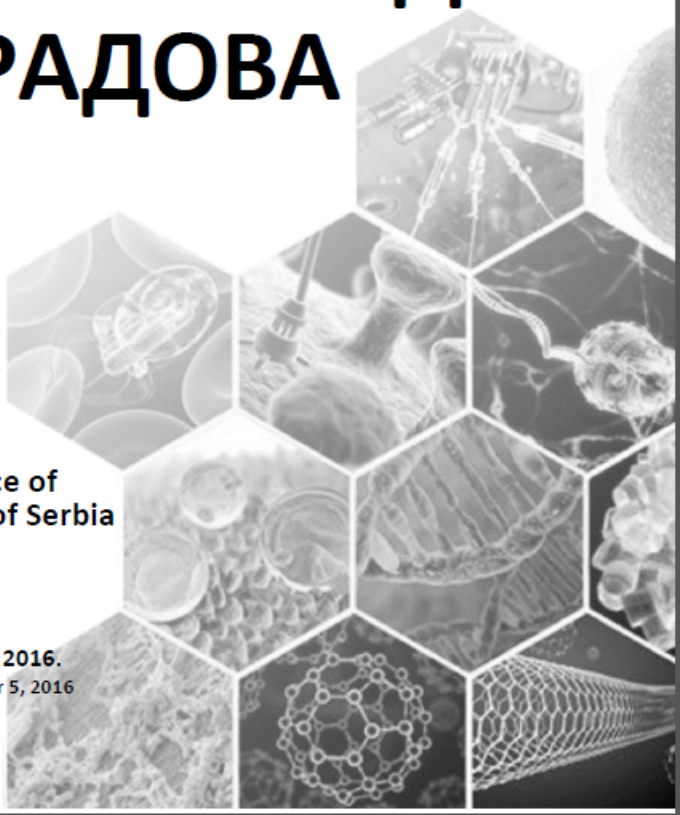
Српско хемијско друштво
Клуб младих хемичара Србије
Serbian Young Chemists' Club

ЧЕТВРТА КОНФЕРЕНЦИЈА МЛАДИХ ХЕМИЧАРА СРБИЈЕ

КРАТКИ ИЗВОДИ РАДОВА



Book of Abstracts

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Teorijsko proučavanje interakcija između HDAC-1 i HDAC-6 enzima i *in silico* dizajniranih inhibitora

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Nesrazmerna posttranslaciona deacetilacija histona je povezana sa nastankom tumora i neurodegenerativnim bolestima. Do sada, FDA je registrovala 5 inhibitora histon deacetilaze (HDAC), koji su okarakterisani kao neselektivni HDAC inhibitori. Koristeći virtuelni dizajn zasnovan na hemijskoj strukturi liganda (3D-QSAR), na primeru naftalimidnog derivata skriptaida, utvrdili smo molekulske karakteristike značajne za selektivnu inhibiciju histon deacetilaze 6. Nakon *in silico* dizajna novih inhibitora, primenili smo molekulski doking koristeći kristalnu strukturu HDAC-1 enzima (5ICN) i kristalnu strukturu drugog katalitičkog domena HDAC-6 enzima (5EDU). Molekulski doking je proučavan u GOLD 5.4.0 softveru, koristeći ChemScore kao skoring funkciju, i dva *in silico* dizajnirana jedinjenja D-48 I D-34 su odabrana kao potencijalni selektivni HDAC-6 inhibitori za sintezu. Kraći linker odabranih jedinjenja omogućuje hidroksamskoj grupi da bude dostupnija Zn^{2+} jonu pri dnu aktivnog mesta enzima. Oba jedinjenja su pokazala poboljšanu selektivnost predviđenu razvijenim 3D-QSAR modelima.

A theoretical study of interaction between HDAC-1 and HDAC-6 enzymes and *in silico* designed inhibitors

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The disproportionate posttranslational histone modification as deacetylation has been associated with tumorigenesis and neurodegenerative diseases. Currently, there are five approved histone deacetylase (HDAC) inhibitors by FDA, which are defined as pan-HDAC inhibitors. By using ligand based virtual design approach (3D-QSAR) based on naphthalimide derivative scriptaid, we found molecular determinants important for selectivity towards histone deacetylase 6 isoform. After in silico design of novel inhibitors, we performed molecular docking studies using crystal structure of HDAC-1 enzyme (5ICN) and crystal structure of second human catalytic domain of HDAC-6 enzyme (5EDU). Molecular docking procedure was performed in GOLD 5.4.0 Software and ChemScore as scoring functions, and two *in silico* designed compounds D-48 and D-34 were selected as potential selective HDAC-6 inhibitors for synthesis. The shorter linker of selected compounds allows hydroxamic group to be more accessible to Zn^{2+} ion at the bottom of the active pocket. Both of them shown improved predicted selectivity according to the developed 3D-QSAR models.