HP-SEE

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for South East Europe's Research Communities

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Book of Abstracts

Edited by: Danica Stojilljkovic, Institute of Physics Belgrade

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Computational Chemistry

Use of High Performance Computing in (Bio)Chemistry

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Presenter:
Ivan O. Juranić, *Department of Chemistry-IChTM, University of Belgrade*

Contribution type: Invited lecture

Abstract

A short overview of computational modeling is presented. The major features of molecular geometry optimization are given, and the computational demands are analyzed. Short outlines of strategies that are in use for speeding-up of computation are presented, too.
In the second part of presentation, the specific examples, and accompanying results of computational applications in chemistry are given. The aim is to make a rational design of efficient drugs, and, on other hand, to explain the mechanisms of complex chemical reactions. In last two centuries of Chemistry, the models are in heart of amazing progress made in it. Many models deal with non-observables, and validity of model can be tested only by simulations. These simulations could be done on various levels of complexity, and some illustrative examples are presented.
A study of molecular potential energy surface (PES) is done on QM level in order to explain the mechanism of the reaction of carbonyl compounds with bromoform. A successful application of non-observable molecular descriptor – partial atomic charges - is presented, too.
The application of MM and MD simulations for the description of interaction of small molecules with proteins was successfully done on several examples. The computationally derived molecular descriptors were used for statistical modeling of the correlation between molecular structure and biological activity of compounds. These correlations give the leverage for the design of more potent drugs.

Dynamics of uninhibited and covalently inhibited cysteine protease on non-physiological pH

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Contribution type: Oral presentation

Abstract

Cysteine proteases involved in degradation of proteins, widespread in plants, parasites and vertebrates, are an important medicinal chemistry target implicated in the diseases ranging from immunological processes to cancer. Due to conserved cysteine residue in their active site, unsaturated ketones and their analogs represent one of the major chemotypes used for inhibitors design [1]. In this communication the dynamics of the papain-like cysteine protease isolated from the fruit, uninhibited and inhibited with covalent inhibitor E-64, on non-physiological pH, were reported merging results and experiences from our biochemical and medicinal chemistry laboratories.The aim of our study is to explain some experimental findings. Proteins are modeled using similar ones with the known 3D structure, taken from Protein Data Bank [2]. After sequence alignment residues that differentiate templates from the experimental proteins were manually changed. Afterward the eventual existence of close contacts, bumps or similar was carefully checked. The protonation states of the aminoacid residues and the inhibitor ionizable groups were adjusted to pH 1.5, using empirical function [3]. Systems were neutralized with explicit counterions, than embed in explicit water, obtaining the sphere having ~ 100 Å radius. Systems under simulations were minimized during 30000 steps, than heated to 300 K during 10000 steps. After equilibration, the 5 ns unconstrained and unbiased molecular dynamics simulation, on 300 ± 10 K, were performed on the each system. CHARMm22 force field and Geisteiger charges were used. Electrostatics was treated by Particle Mesh Ewald method. The periodic boundary conditions were applied, and 12 Å cut-off (8 Å switching), with pair list distances set to 13.5 Å. Each simulation was performed in duplicate, using different random seeds and giving comparable results. The root-mean-square deviation of the backbone atoms and the energy profiles of the systems under the study proved stable, converged simulation. The movement of the loops and the (flexible) inhibitor, as well as radius of gyration of the selected amino-acid side chains was analyzed and conclusion derived on the influence of the covalently bound inhibitors on the dynamics of the enzyme on pH 1.5. All calculations were performed by NAMD 2.8 [4] on the multimode Linux cluster. For the preparation of the systems, and analysis of the results VegaZZ 2.4.0 were used [5].

References: [1] Mini-Rev. Med. Chem. 7 (2007) 1040; [2] J. Mol. Biol. 112 (1977) 535; [3] Proteins 73 (2008) 765; [4] J. Compt. Chem. 26 (2005) 1781; [5] J. Comp. Aided Mol. Des. 18 (2004) 167

Free-energy surfaces of 2-[(carboxymethyl)sulfanyl]-4-oxo-4-arylbutanoic acids. Molecular dynamics study in explicit solvents.

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Contribution type: Oral presentation

Abstract

The 2-[(carboxymethyl)sulfanyl]-4-oxo-4-arylbutanoic acids (Scheme 1) exert antiproliferative potency and significant selectivity toward human tumor cells in vitro in low micromolar to submicromolar concentrations [1]. In the congeneric set of compounds we observed the regularity between the selectivity and the properties derived from the conformational assemblies of compounds [2]. As the part of ongoing studies, in this communication we repot the free-energy surfaces of the representative congeners, as obtained by molecular dynamics simulations, using adaptive biasing force (ABF) procedure [3] to speed-up sampling of the systems. All simulations were performed involving simulation of explicit solvents having different polarity and hydrogen bond donor/acceptor abilities (water, chloroform, dimethyl-sulfoxide, ethanol, n-octanol/water mixture), lasting from 20 to 50 ns. For comparison, the molecular dynamics simulations on the representative system without applied biasing forces was also reported. The differences in the free-energy surfaces of the same, representative, congener in different solvents reflect the fact that flexible molecules change conformations in a way to mimic surroundings (i.e. solvent in which are dissolved) [4]. Ranges of property spaces [5] of compounds under the study were analyzed and compared. In all simulations molecules were treated in their neutral form. The effect of using different types of atomic charges on the final results is also commented. All systems under the study were minimized during 20000 steps, than heated to 310 K for 10000 steps. Molecular dynamics simulation, on 310 ± 10 K, with applied ABF procedure was performed on the each system. CHARMm22 force field and Geisteiger charges, or charges derived from the semiempirical calculations, were used. Electrostatics was treated by Particle Mesh Ewald method. The periodic boundary conditions were applied, and 12 Å cut-off (8 Å switching), with pair list distances set to 13.5 Å. All calculations were performed by NAMD 2.8 [6] on the multimode Linux cluster. For the preparation of the systems and analysis of the results VegaZZ 2.4.0 was used [7].

References: [1] J. Med. Chem. 48 (2005) 5600; [2] a) The 18th European Symposium on Quantitative Structure-Activity Relationships, Book of Abstracts, pp. 278-279, Greece, 2010; b) The 19th European Symposium on Quantitative Structure-Activity Relationships, Book of Abstracts, p 147, Austria, 2012; [3] J. Chem. Theory Comput. 6 (2010) 35; [4] Med. Res. Rev. 17 (1997) 303; [5] J. Med. Chem. 48 (2005) 4947; [6] J. Compt. Chem. 26 (2005) 1781; [7] J. Comp. Aided Mol. Des. 18 (2004) 167

In the search of the HDAC-1 inhibitors. The preliminary results of ligand based virtual screening.

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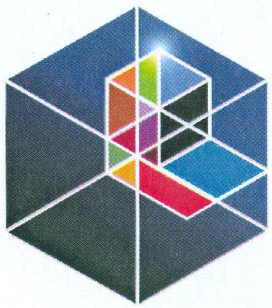
Contribution type: Oral presentation

Abstract

Acetylation and deacetylation of histone is an important mechanism to regulate the DNA expression. Two main classes of enzymes catalyze this regulatory mechanism: histone acetyltransferase (HAT) and histone deacetylase (HDAC). HDACs are involved in signal transduction, cell growth and cancer [1]. We report the results of the preliminary ligand-based virtual screening in the search of the novel HDAC-1 inhibitors. By this virtual screening study, we aimed to test the performances of the OpenEye applications installed on our home cluster PARADOX. As the template, we used the ligand from 3MAX PDB entry [2]. The ChemBank set of 2346 molecules was taken from the ligand.info [3]. After the filtering (exclusion of the metal containing compounds, and limiting of the number of HBA (10) and HBD (5)) we obtained 1990 molecules, which are submitted to OMEGA [4] to generate conformational assemblies of the molecules studied. The OMEGA options were set to default, yielding ~ 142000 conformers in total. We searched the shape and the pharmacophoric similarity of the multiconformer ligand set against the template molecule by ROCS program [5]. The best-ranked solution of the 100 hits by TanimotoCombo score (1.305) was Nifenazone, that has been used as the analgesic drug and was withdrawn due to heavy side effects. The subset of ligand conformers prepared with ROCS is further submitted to EON [6], to search for the electrostatic similarity to the template molecule. The compound labeled as the itdac-7 in ChemBank appears as the best-ranked solution by the ET-combo score (1.403) maid. There is no literature data on this compound, but ChemBank results from the high-throughput screening campaigns indicates itdac-7 as active toward enzymes involved in deacetylation. Our preliminary screen, as reported in this communication, involves the MMFF94s charges ascribed by default. Further work will be directed to assignation of the semiempirical charges for the electrostatic similarity screen, using the larger database of the compounds. All calculations by OpenEye applications were performed in BJD work group on PARADOX cluster, Institute of Physics, Belgrade.

References: [1] Nature 389 (1997) 349; [2] Bioorg. Med. Chem. Lett. 20 (2010) 3142; [3] Comb. Chem. High. Throughput Screen. 7 (2004) 757; [4] J. Chem. Inf. Model. 50 (2010) 572, OMEGA 2.4.2; [5] J. Med. Chem. 48 (2005) 1489, ROCS 3.1.1; [6] EON 2.0.1, OpenEye Scientific Software, Inc., Santa Fe, NM, USA, www.eyesopen.com .



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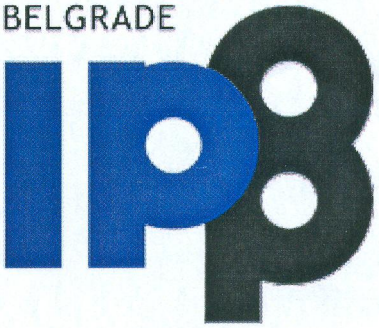

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October 17-19, 2012, Belgrade

Ivan JURANIC

Faculty of Chemistry, University of Belgrade

presented an Invited Lecture entitled:

Use of High Performance Computing in (Bio)Chemistry

Aneta Karaivanova
Programme Committee Chair

Ioannis Liabotis
HP-SEE Project
Technical Coordinator

Mihnea Dulea
Programme Committee Chair

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Branko J. DRAKULIC

Department of Chemistry-IChTM, University of Belgrade

presented a Contributed Talk entitled:

Dynamics of Uninhibited and Covalently Inhibited Cysteine Protease on Non-Physiological pH

Aneta Karaivanova	Ioannis Liabotis	Mihnea Dulea
Programme Committee Chair	HP-SEE Project Technical Coordinator	Programme Committee Chair

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Ilija N. CVIJETIC

Innovation Center of the Faculty of Chemistry
University of Belgrade

presented a Contributed Talk entitled:

In the Search of the HDAC-1 Inhibitors. The Preliminary Results of Ligand Based Virtual Screening.

Aneta Karaivanova
Programme Committee Chair

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