OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Omics Studies

September 04-05, 2013 Holiday Inn Orlando International Airport, Orlando, FL, USA

In-Silico combination of docking, QM/MM analysis and MD simulations for tetrahydrobiopterin analogous: Binding towards non-heme active site of phenylalanine hydroxylase and a313t mutant type for neurological cascades

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Phenylalanine hydroxylase (PAH) belongs to tetrahydrobiopterin (BH_4) dependent aromatic amino acid hydroxylases enzyme family in which BH4 is an important protein co-factor which promotes hydroxylation of neurotransmitters. Hence, BH4 deficiency leads to imbalance in neurotransmitters synthesis and thus causes neurological disorders. In present study we have utilized *in-silico* methodology for modifications in parent skeleton of nonreduced BH_2 on the basis combined analysis via Docking, QM/MM analysis and MD simulations, best pose of high affinity co-factor was obtained and QM/MM optimization leads to square-pyramidal coordination of non-heme active site. The specific recognition of protein target showing binding similarity of modified analogues with natural nonreduced co-factor. We have studied the binding of various structurally modified co-factor (dihydrobiopetrin) analogues with phenylalanine hydroxylase enzyme and its A313T mutant via docking studies. The altered co-factors were found to show interactions with important phenylalanine hydroxylases residues: Arg270, Glu280, Thr278, Pro279, Gly346, Ser349, Glu353, Val379 and Fe425 After the docking of these modified molecules with PAH molecules with high affinity were subjected for further analysis with the mutant phenylalanine hydroxylase enzyme. Hence, results suggested the therapeutic application of these modified co-factors. Also, for these metalloproteins, QM/MM and MD simulations analysis revealed the coordination environment of active site and thus depicted more descriptive abilities for it. The structural and energetic information obtained from the time-averaged 200ps MD simulation of co-factor-metalloprotein complex results helped understand that co-factor binding do not perturb the coordination environment of iron residing in 2-Histdine and 1-Glutamate triad. QM/MM optimization showed promising picture of active site QM environment which remained stable during whole 200ps simulations. Thus, we can conclude that these compounds could be potential selective co-factors of PAH amino acid hydroxylases that can be experimentally validated. Therefore, the acceptability of these analogues can be validated by synthesis and *in vitro* approaches to investigate their biological activity to validate our *in-silico* results.

Biography

Nidhi Chadha is pursuing her Ph.D. from University of Delhi and INMAS, Delhi. Her educational background is M.Sc in physical chemistry and more than 2 year experience in computational science which includes various levels of calculations in the area of drug designing in experimental and theoretical calculations. She has published her work in international reputed journals.