OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing

October 15-17, 2013 Hampton Inn Tropicana, Las Vegas, NV, USA

The importance of tetrahydrobiopterin mediated interactions in aromatic amino acid hydroxylases enzymes family: Assessing effect on biosynthesis due to effect of single site mutation on thermodynamic stability of hydroxylases

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Introduction: The mammalian aromatic amino acid hydroxylases (AAHs), including phenylalanine hydroxylase (PheOH), tyrosine hydroxylase (TyrOH) and tryptophan hydroxylase (TrpOH), are involved in important metabolic pathways neurotransmitters. These BH_4 dependent systems utilised BH_4 as protein co-factor and thus promotes hydroxylation reactions. Subsequently, defects during regeneration or in biosynthesis leads to BH_4 deficiency which has been reported in various neurological disorders such as phenylketonuria, Parkinson's disease and neuropsychiatric syndromes. Lower activities of these enzymes result in lower levels of catecholamine in various neurological disease states, including depression, hypertension and schizophrenia. Therefore, biosynthesis of neurotransmitters is important to study for the identification of aspects of defects in the pathways. In the present study we have utilized single site mutation induced effects on three aromatic amino acid hydroxylases of the metabolism pathway to study effects on biosynthetic pathways.

Materials and methods: For the present computational studies, we have utilized atomic coordinates of AAHs PDBs, 1MLW (hTrpOH), 1DMW (hPheOH), 2TOH (rTyrOH) and IMMK, from RCSB PDB. All the PDB's structures were prepared. For mutational analysis the PoPMuSiC program was utilized to introduce single site mutations in these hydroxylases and to calculate the resulting changes in folding energy changes ($\Delta\Delta G$) in wild type and mutated protein. Neurotransmitters i.e. dopamine, L-DOPA, epinephrine, melatonin, norepinephrine, serotonin, tyrosine, tryptophan and phenylalanine and BH4 were used for docking.

Results and discussion: The effects of single site point mutation on the stability of three hydroxylases, hPheOH, rTyrOH and hTrpOH, along with one ternary complex of hPheOH were analyzed in PoPMuSiC program. In all four cases, we have analysed two sets for each desired residue: one with highest and lowest $\Delta\Delta G$ values. This was done so as include range of lowest to highest stability of these hydroxylases on single site mutations. Also, average $\Delta\Delta G$ values are reported in kcal/mol. Analysis of BH4 binding, active site evaluation (iron coordinated ligand), substrates specificity determinates residues and residues importance and structural preference share by enzymes studied from mutational analysis was done.

Conclusion: In conclusion, present study was dwelled into the aspects of mutational analysis of aromatic acid hydroxylases for the evaluation of effect on biosynthetic pathways. Further, future studies will be done for the post docking processing ligand and co-factor binding studies.

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