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Pharmacophore based virtual screening and building of 3D-QSAR in the discovery of new cathepsin K inhibitors

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For the therapeutic optimization of various cancers such as breast cancer, prostate cancer, thyroid carcinoma, lung adenocarcinoma targeting the predominant papain-like cysteine protease Cathepsin K is found to be dominant strategy. In current study, designing of Cathepsin K inhibitors through pharmacophore and virtual screening methodology displayed promising number of scaffolds. A five point pharmacophore with two hydrogen bond acceptors (A), one hydrogen bond donor (D), one hydrophobic feature (H) and one ring feature (R) as pharmacophoric features were developed to understand active scaffolds with specific functional groups. Validation of the pharmacophore hypothesis was carried out with enrichment statistical calculation. The best pharmacophore model has shown best fitness against 100 active molecules with PIC_{50} values greater than 8 among 254 active molecules. Further, it yielded a statistically significant 3D-QSAR model with a correlation coefficient of R^2 = 0.901 for training set compounds and with test set correlation coefficient of Q^2 = 0.823, the generated model showed excellent contour map predictions. The model was then employed as 3D search query to screen against private and public compound libraries (BITS, Asinex database) followed by virtual screening which resulted in 322 molecule hits. Inhibitors having above 50 percent oral bioavailability predicted through Qikprop were chosen for biological activity assays. Molecules which have shown enzyme inhibition at nano-molar concentration were considered as potential selective non-covalent inhibitors for Cathepsin K.

Biography

Sridevi Kondepudi is pursuing her B.Pharmacy (Hons.) from BITS-Pilani, Hyderabad campus. Currently she is working on a lab oriented project in Computer-aided drug discovery lab at BITS Hyderabad. She has been placed as Trainee in Mylan laboratories Ltd.

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Immobilization of Glycine max amylase onto activated woven Bomybx mori silk fabric

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Silk fibers in the form of woven fabric were used as a novel and inexpensive carrier for the immobilization. Fibrous silk has a large surface area, high mechanical strength and good compatibility which are advantageous to the use as a support for the enzyme immobilization. Silk biomaterials are biocompatible and can be chemically modified through amino acid side chains to alter surface properties for immobilizing the cellular growth factors. Woven Bombyx mori silk fabric have excellent properties in diffusivity of substrates, mechanical strength, and handling. The amino group enrichment of Bombyx mori silk fabric was made by the treatment of chlorinated silk fabric with 2-aminoethanethiol (AET) and poly(ethylenimine) (PEI). Although the method of immobilization of alkaline phospatase onto Bombyx mori silk fibroin are available such as immobilized was by covalent bond formation by diazo and cyanogen bromide onto partially hydrolyzed silk fabrics by using diazo, adsorption, glutaraledyde and azide methods. As well as the other enzymes such as glucose oxidase (GOD) was immobilized on the nonwoven fabrics with Bombyx mori silk fibroin gel, viscose rayon, poly-ethyleneterephthalate, 6-nylon, and polypropylene with activated surface by fluoline treatment. However, all these methods were expensive methods as it required tedious techniques for activation of silk fabric and required costly equipments as well as commercial enzyme. But, in this work, we describe the immobilization of amylase which is extracted from Glycine Max (soybeans) onto aminated-chlorinated woven Bombyx mori silk fabric through covalent coupling with glutraraldehyde method which was given by Avrameas, 1969. As well as kinetic properties of immobilized enzymes were studied. In the present report, we described the covalent coupling of glycine max amylase onto aminated/ chlorinated woven Bombyx Mori silk fabric and this coupling suppresses the thermal denaturation of bound enzyme as well as bound enzyme becomes more resistant to fungal and bacterial attack. The enzyme immobilized onto activated woven Bombyx mori silk fabric was showed fairly good storage stability of 2 months. The kinetic properties are compared with that of free enzymes.

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