DOCKING STUDIES OF CURCUMIN AND ANALOGUES WITH VARIOUS PHOSPHODIESTERASE 4 SUBTYPES

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Abstract

Aims and Objectives: The primary aim of this study is to understand the binding of curcumin and its analogues to different PDE4 subtypes. The identification of the role of PDE4 subtype inhibition in the anti-inflammatory property of curcumin will be the second objective of this study. *In silico* docking study and docking analysis will be demonstrated to provide required structural information for designation of curcumin derivatives with better anti-inflammatory activity.

Materials and Method: Curcumin and its analogues were chosen as ligands and subjected to docking studies using PDE4A, PDE4B, PDE4C and PDE4D as the target receptor. A data set comprising of 18 compounds of curcumin and analogues was used as ligands for docking of PDE4 subtypes. Co-crystallised curcumin in Protein 4PMF retrieved from Protein Data Bank was obtained using BIOVA Discovery Studio 2017 R2 and used as standard. ACD/ChemSketch Version 12 was used to draw all structures of curcumin and analogue compounds in training set and the test set. Docking results were obtained using AutoDock 4.2.6 software and AutoDock Vina 1.1.2 software integrated in LigandScout 4.1. During this process water molecules were removed from proteins, charges were added and receptor structures were minimized by applying suitable force fields. The results were tabulated and compared, the ratio of selectivity of all compounds between PDE4B and PDE4D were calculated as well. The interaction energies of the ligands provided information about selectivity of ligands for the receptor subtypes.

Key Finding: All curcumin analogues used for this study have good binding affinity with all PDE4 subtypes, with evident selectivity towards PDE4B subtype. The binding of analogue A11 provides the highest binding energy among all ligands.

Conclusions: Curcumin and analogues have moderate to strong potency to inhibit activity of PDE4 and have evident selectivity towards PDE4B subtype. Oxygen atom of methoxy groups plays a major role in protein binding and alterations made on this aryl side chain could interfere with the protein binding. Tetrahydropyran side chain and heterocyclic rings are suggested to aid in protein binding. Curcumin anti-inflammatory property while retaining non-toxic profile can be correlated with the selectivity towards PDE4B subtype, which is the main therapeutic target for major inflammatory diseases.

KEYWORDS: PDE4B selectivity, docking study, curcumin and analogues, anti-inflammatory property