Identification of 'Small Molecule Activators' to Enhance Remyelination through Neuregulin 1- ErbB Signaling*in silico*

A Thesis Submitted to

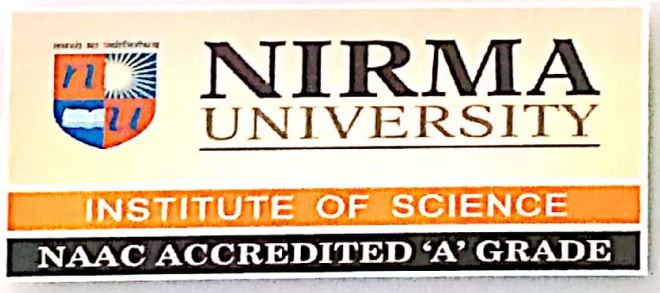
NIRMA UNIVERSITY

In partial fulfillment of the award of the Degree of

MASTERS OF SCIENCE

IN

MICROBIOLOGY



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CERTIFICATE

This is to certify that the thesis entitled "*Identification of 'small molecule activators' to enhance Remyelination through Neuregulin1 / ErbB Signaling in silico*" submitted to the **Institute of Science, Nirma University** in partial fulfillment of the requirement for the award of the degree of **M.Sc Microbiology**, is a record research work carried out by **Ms. Sakshi Singh (15MMB013) and Shivani Patel (15MMB017)** under the guidance of **Dr. Amee K Nair.** No part of the thesis has been submitted for any other degree or diploma.

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Declaration

The above dissertation project was carried out by **Ms. Sakshi Singh** and **Ms. Shivani Patel** under my guidance.

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ABSTRACT

Myelination is the process in which myelin sheath wraps around the axons. In CNS, oligodendrocytes generate myelin sheath. Myelin sheath promotes the rapid impulse propogation due to Saltatory conduction which facilitate efficient and integrated sensory, motor and higher order cognitive function. In demyelinating diseases, damage to the myelin sheath can be due to defects in myelin metabolism, effect of toxins or damage to oligodendrocytes. Remyelination in CNS is critical because of the poor regenerative potential of oligodendrocytes, the failure of their recruitment at the site of damage and damage due to ROS. NRG1/ErbB signaling ErbB signaling plays a vital role in oligodendrocytes differentiation and myelination. The rationale behind our studies is to identify activator molecules to enhance remyelination by activating NRG1/ErbB signaling. Phytochemicals were selected on the basis of their neuroprotective and antioxidant properties. The chemicals used to prepare the library were already reported to activate tyrosine kinase families other than ErbB tyrosine kinase family. The libraries were screened using AutoDock vina. The compounds were docked on ErbB4 tyrosine kinase domain and their binding energy were analysed. The successfully docked compounds were subjected to ADMET prediction. The pharmacokinectic properties and their oral bioavailabity were assessed via ADMET prediction tools: Molinspiration and SwissADME. .We have identified Huperzine, Mitrinermine, Melatonin and Ephedrine as potential activators of NRG1/ErbB signaling in CNS. The best pharmacophore generated with these compounds have the scores 15.432 and 12.700.Curcumin, Cyanidin Chloride, Gingkolide A, Hesperetin Dihydrochalcone, Hesperetin, Hesperetin triacetate, Huperzine, Melatonin, Mitrinermine, Naringenin, Pelargonidin and Deoxygeduninshowed negative kinase inhibition activity but they can not penetrate the BBB therefore, they can be used for activating NRG1/ErbB signaling in PNS in future.Hesperetin, Hesperetin dihydrochalcone, Hesperetin triacetate and Pelargonidin, Cyanidin chloride, Hesperetin dihydrochalcone, Hesperetin triacetate, Hesperetin, Naringenin were the compounds that form the best pharmacophore. The scores are 37.477 and 36.00.