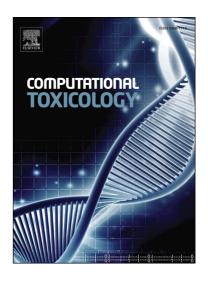
## Accepted Manuscript

Identification of Small Molecule Activators for ErbB 4 receptor to Enhance Oligodendrocytes Regeneration by *In Silico* Approach

Madhavi Joshi, Sakshi Singh, Shivani Patel, Dhriti Shah, Amee Krishnakumar

PII:	S2468-1113(18)30002-1
DOI:	https://doi.org/10.1016/j.comtox.2018.08.004
Reference:	COMTOX 50
To appear in:	Computational Toxicology
Received Date:	5 February 2018
Revised Date:	22 June 2018
Accepted Date:	17 August 2018



Please cite this article as: M. Joshi, S. Singh, S. Patel, D. Shah, A. Krishnakumar, Identification of Small Molecule Activators for ErbB 4 receptor to Enhance Oligodendrocytes Regeneration by *In Silico* Approach, *Computational Toxicology* (2018), doi: https://doi.org/10.1016/j.comtox.2018.08.004

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## ACCEPTED MANUSCRIPT Identification of Small Molecule Activators for ErbB 4 receptor to Enhance 1 **Oligodendrocytes Regeneration by** *In Silico* Approach 2 3 Madhavi Joshi, Sakshi Singh, Shivani Patel, Dhriti Shah and Amee Krishnakumar\* 4 Institute of Science, Nirma University, Ahmedabad -382481, Gujarat, India 5 6 \*Corresponding Author 7 8 **Correspondence Address** Dr. Amee Krishnakumar 9 Institute of Science 10 Nirma University 11 Ahmedabad – 382481, Gujarat, INDIA 12 E-mail: ameenair@nirmauni.ac.in 13 amee14@gmail.com 14 Tel.: +91 484- 2575588, 2576267 15 Fax: +91 484- 2575588, 2576699 16 17

## Introduction 18

demyelination, axons experience substantial physiological changes and molecular During 19 reorganizations due to loss of myelin sheath which surrounds the axons [1]. In CNS, oligodendrocytes are 20 critically involved in the formation of myelin sheath responsible for saltatory impulse conduction [2]. Myelin 21 producing oligodendrocytes are vulnerable to free radicals, inflammatory response, excitotoxicity due to its high 22 metabolic rate [1] and creating non conducive environment in oligodendrocyte. It causes abnormal distribution 23 of ion channels, across the axons leading to improper ion transport and ultimately poor impulse propagation [3] 24 which evoke demyelination. In CNS, oligodendrocytes have limited regenerative potential to overcome this 25 suboptimal regeneration. Triggered damage will lead to apoptosis and autophagy of oligodendrocytes and 26 damage the spared axons [1]. 27

SCRIP

Epidermal Growth Factor (ErbB) receptors are involved in Neuregulin 1 (NRG 1) mediated 28 proliferation, differentiation and migration of oligodendrocytes [4]. They control myelin production by 29 oligodendrocytes during developmental as well as adult stage [5]. Impaired ErbB signaling thus alters the 30 31 oligodendrocytes morphology, myelin thickness and may cause slower impulse conduction velocity in CNS axons [6]. Role of NRG1/ErbB signaling has been undisputed and well portrayed in multiple sclerosis, 32 schizophrenia, neuropathy [7]–[10]. Hence, we focused our studies to search for activators that can enhance the 33 signaling of NRG 1 through ErbB receptor and ultimately aim to improve oligodendrocyte regeneration. 34

35 ErbB receptors are trans-membrane tyrosine kinases activated by ligand induced dimerization [11]. The ErbB receptor contains an extracellular ligand-binding domain, a trans-membrane domain, a juxta membrane 36 domain, a kinase domain, and a COOH terminal tail (C-terminal tail) as shown in Figure 1. The kinase domain 37 adopts a bi-lobular structure consisting of an N-terminal ATP-binding site and a C terminal substrate binding 38 site [12]. Ligand binding on allosteric site of tyrosine kinase domain induces dimerization of ErbB receptors 39

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