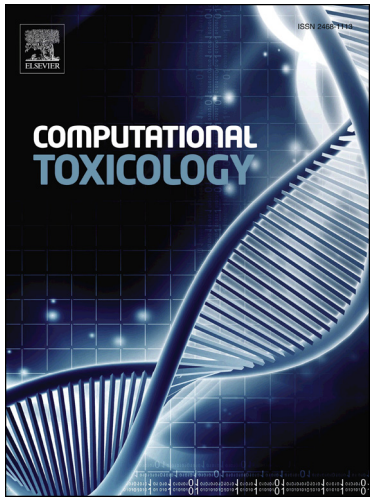

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Introduction

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

Epidermal Growth Factor (ErbB) receptors are involved in Neuregulin 1 (NRG 1) mediated proliferation, differentiation and migration of oligodendrocytes [4]. They control myelin production by oligodendrocytes during developmental as well as adult stage [5]. Impaired ErbB signaling thus alters the 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, schizophrenia, neuropathy [7]–[10]. Hence, we focused our studies to search for activators that can enhance the signaling of NRG 1 through ErbB receptor and ultimately aim to improve oligodendrocyte regeneration.

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 domain, a kinase domain, and a COOH terminal tail (C-terminal tail) as shown in Figure 1. The kinase domain adopts a bi-lobular structure consisting of an N-terminal ATP-binding site and a C terminal substrate binding site [12]. Ligand binding on allosteric site of tyrosine kinase domain induces dimerization of ErbB receptors