UNIVERSITI TEKNOLOGI MARA

DESIGN AND SYNTHESIS OF SACLOFEN ZINC (II) COMPLEX

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CHAPTER 1

INTRODUCTION

1.0 Research background

γ-Amino butyric acid (GABA) plays an important role in the migration of neuron where the GABA analogues give effects on 3 types of receptors that are $GABA_A$, $GABA_B$, and $GABA_C$ (Behar et al. 1996). GABA predominantly acts as chemoattractant where it involves in the migration and development of the embryonic cortical cells (Behar et al. 2001). GABA is the dominant inhibitor of neurotransmitter in mammalian where it affects the synaptic integration, depolarization of neuron and also the network oscillation that contribute to the functional of cognition in human (Gaiarsa and Porcher 2013).

Saclofen with IUPAC name 3-Amino-2-(4-Chlorophenyl) Propylsulfonic Acid is an analogue of baclofen which antagonize $GABA_B$ receptor (Kerr et al. 1989). Saclofen is the substitution of Baclofen's carboxylic group with Sulfonic Acid. The effect of saclofen is mainly in the brain where it can inhibit the cell migration and of embryonic corticol cell migration (Behar et al. 2001). Saclofen also gives effect on cardiac and renal or any part of the body that has $GABA_B$ receptor. Even though it affects the brain but, saclofen that play it roles in basal ganglia does not affect the sleeping time when tested on rat (Roffler 2012). Saclofen gives it effect on brain by altering the level of Ca^{2+} (Maric et al. 2001). Saclofen when react with GABA

receptor plays a role in nitric oxide level in the brain that will affect neurodegeneration (Kimura-Kuroiwa K et al. 2011).

The combination of metal and macrocyclic tetraamine had been extensively studied and gain interest in research area due to its therapeutic advantage and also as detection probes. Zinc (Zn) is a metal that knowns as 'essential trace element' where it plays necessary roles in human health ("Zinc: MedlinePlus Supplements" 2014). Zn deficiency can results in many disease. Zn also plays an important part in the brain (Bossy-Wetzel et al. 2004). Zn can reduce Nitric Oxide (NO) production in the cell (Cortese-Krott et al. 2014). Cyclen shows high affinities towards transition metal ions and the combination of it can had been proved to play roles in DNA and RNA cleavage and also some other effect (Huang et al. 2007).

1.2 Problem Statement

The administration of saclofen alone does not reduce the volume of nitric oxide in the brain and the existence of Zn^{2+} in free form causes neurodegenerative which this can be achieved by using cyclen that combine with saclofen to achieve the desired outcome where cyclen acts as coordinator of Zn^{2+}. The interest in this research is to know how the synthesis of Zn^{2+}- cyclen with saclofen by using pendant that attached at amide group can form complex in order to give the desire therapeutic outcome where it may reduce or prevent neurodegeneration.