UNIVERSITI TEKNOLOGI MARA

DESIGN AND SYNTHESIS OF WR-1065 Zn^{2+}-CYCLEN COMPLEX

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Table of Contents

ABSTRACT

WR-1065 is active metabolite of amifostine that activate p53 protein to bind with consensus DNA. However, individual with replacement of cysteine with serine has reduces in p53 binding activity to target DNA. Additional of Zn^{2+} ions have significant role in regulation of p53 protein binding to specific target DNA while a novel prototype of Zn^{2+}-cyclen derivatives had widely being used in DNA recognition. The aim of this study were to design and synthesis WR-1065 Zn^{2+}-cyclen complex as a new chemical entity and further complexation of Zn^{2+} ions with WR-1065 cyclen complex. The consequences objective was to study the DNA binding properties of WR-1065 Zn^{2+}-cyclen complex by using natural calf-thymus DNA. The methodologies involved seven-step synthesis of WR-1065 appended with Zn^{2+}-cyclen complex with bromoethane as a ligand that linked through S_N2 mechanism. First, 1, 4, 7, 10-tetraazacyclododecane or free cyclen was protected with $(Boc)_2O$ with ratio of free cyclen/$(Boc)_2O$ at 1:2.8. The major product form is 3-Boc cyclen. Second step was reaction with bromoethane to form 3-Boc cylen appended bromoethane. This compound was then undergo bromination step by N-bromosuccinimide (NBS) through free radical mechanism. The product of bromination was then linked with WR-1065 through bromine atom substitution. The intermediates of all compounds were characterized by thin layer chromatography (TLC) and further confirmation by NMR spectroscopy (^1H). The half part of synthesis of WR-1065 appended Zn^{2+}-cyclen complex through S_N2 mechanism shows positive result. However, the result for bromination step with NBS led to low percentage yield. Thus, the final product could not be synthesized due to scarce of material; hence DNA binding property of final product cannot be identified.

CHAPTER 1

INTRODUCTION

1.1 Background of study

Amifostine is a protective compound in cancer treatment that capable to reduce or eliminate the side effects of radiotherapy and chemotherapy (Diana & Smardova, 2007). The main active metabolite of amifostine is free thiol, WR-1065, that responsible for cytoprotective effects. Amifostine cannot mediate cytoprotection without being metabolizes into its metabolite which is WR-1065 because WR-1065 easily penetrates the cell while amifostine is not capable to penetrate the cell easily (Hensley et al., 2009). A stress signal from amifostine metabolite, WR-1065 is transmitted through p53 protein by post-translational modification (Harris & Levine, 2005). Activation of p53 protein leads to either cell cycle arrest or cellular apoptosis in cancer cell (Jin & Levine, 2001). Free sulfhydryl group in WR-1065 directly interacts with p53 and modifies p53 cysteine residues. Activation of p53 by WR-1065 increased the binding of functional p53 protein to consensus target DNA sequences and increased its transcription activity of specific genes (Pluquet, North, Richard, & Hainaut, 2003).