UNIVERSITI TEKNOLOGI MARA

STUDIES TOWARDS THE TOTAL SYNTHESIS OF *CIS*-OSELTAMIVIR PHOSPHATE AND ASYMMETRIC SYNTHESIS OF *CIS* γ-BUTYROLACTONE-LACTAM DERIVATIVES

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ABSTRACT

Oseltamivir phosphate (Tamiflu) is the prodrug of a potent viral neuraminidase inhibitor and has been utilized as an effective treatment and preventative for influenza A and influenza B. Due to the concerns about a potential pandemic influenza outbreak and the limited availability of (-)-shikimic acid, organic chemists have shown significant interest in synthesising oseltamivir using alternative synthetic approaches. In this study, we embark on developing a synthetic target molecule, a novel structure of *cis*-oseltamivir phosphate, *cis* **1d** as a new potential anti-influenza drug starting from simple, cheap and commercially available starting materials, in part A. In this part, the intermediate towards formation of *cis*-oseltamivir phosphate, (1*S*,6*R*)-3-cyano-6-hydroxy-5-(pentan-3-yloxy)cyclohex-3-en-1-yl)carbamate **16** was synthesised from 1,4-cyclohexadiene **5** via a novel and new sequence synthetic route. A unique feature of this synthesis is that the intermediate was synthesised from a readily available cyclohexene ring system by sequentially inserting substituents; an amino group at the carbon-1 position, a hydroxy group at the carbon-6 position, a pentaneyloxy group at the carbon-5 position, and a cyano group at the carbon-3 position sequentially through 8 reaction steps. The synthesis of the carbon-1 substituent involved epoxidation of 1,4-cyclohexadiene **5** and catalytic asymmetric ring opening by the salen complex and $TMSN_3$ to afford azide **8**. The formation of carbon-6 hydroxyl group was achieved after one pot reduction and amine protection of azide **8**. The allylic position of olefin at the carbon-5 was an active site for constructing a pentaneyloxy group via allylic oxidation of compound **10** using SeO_2 in the presence of TBHP and etherification of compound **12** with 3-pentanol. The cyano group at the carbon-3 position in compound 16 was successfully developed after the treatment of compound **13** by epoxidation of olefin, ring opening by TMSCN and elimination reaction. Then there were two more steps left, the Mitsonubu reaction and hydrolysis to targeted *cis* **1d**. To further expand the use of selected synthetic steps and products from Part A, compounds **10** and **13** were utilized to construct an intermediate compound for Geismann-Waiss lactone (GWL) synthesis. In part B, the synthesis of *cis* γ-butyrolactone-lactam derivatives as potential GWL's intermediates were examined. The oxidative cleavage of alkene by ruthenium tetraoxide, lactonization and lactamization on compounds **10** and **13** successfully produced compounds **18** and **19** in good yield. As conclusion, we have developed eight (8) reaction steps to afford compound **16** in part A and two new compounds of **18** and **19** in part B.

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TABLE OF CONTENTS

CHAPTER ONE
INTRODUCTION

1.1 Influenza Outbreak and Treatment Methods

The influenza virus, usually referred to as "the flu," causes serious and contagious viral infection of the respiratory system. Influenza virus infections occur every year in both the northern and southern hemispheres, primarily during the winter. However, in tropical nations, it can also occur throughout the year, resulting in a seasonal epidemic influenza (Singh et al., 2019). The seasonal influenza affects 20 to 30% of the child population and up to 10% of the adult population globally (World Health Organization [WHO], 2021, October 2021). According to WHO (2021, October 13), seasonal influenza outbreaks caused an estimated annual death toll of approximately 290,000 to 650,000 annually. In addition to seasonal influenza, the world is currently facing antigenic shifts caused by the formation of a new and substantially distinct influenza virus, which may result in an influenza pandemic.

There have been four pandemics brought on by the spread of novel influenza strains: the H1N1 Spanish flu in 1918 (resulting in 50 million fatalities), the H2N2 Asian flu in 1957 (resulting in 2 million fatalities), the H3N2 Hong Kong flu in 1968 (resulting 1 million fatalities), and the H1N1 swine flu in 2009 (resulting in 284,000 fatalities) (Nickol & Kindrachuk, 2019). Currently, avian influenza viruses continue to pose a threat to human and animal health. Viruses of the H5 and H7 subtypes, which have the hemagglutinin (HA) gene, have caused 2634 human cases worldwide, with over 1000 fatalities (Shi et al., 2023). Since the first human case reported in 1997, H5 influenza viruses have caused numerous, often serious, human infections (Lai et al. 2016). A highly aggressive form of influenza virus, such as H5N1, could potentially mutate to become easily transmissible between humans and trigger another devastating pandemic, similar to the current pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection (Cai et al., 2020; Ding et al., 2020). Avian influenza, as a potential pandemic hazard, is a global concern. This situation emphasizes the importance of continually developing and producing