Chapter 1

Introduction

1.1 Background

Chikungunya virus (CHIKV) is an arbovirus endemic to tropical and subtropical regions such as Africa, South and Central America, as well as in Asia (CDC, 2024). Chikungunya virus is primarily transmitted by *Aedes* mosquitoes, and co-circulate with Dengue and Zika viruses. Once infected, the virus causes a fever with polyarthralgia, and polyarthritis (WHO, 2022). In approximately 40% of cases, the signature musculoskeletal symptoms of chikungunya fever can persist for more than 3 months, deteriorating into more severe and limiting manifestations such as neuropathic pain, rheumatoid arthritis, and bone erosions (Amaral et al., 2019; Ng et al., 2024). Such cases are known as a condition called chronic Chikungunya disease (CCD), which are mostly found in those of extreme ages.

Despite this gravity, the management options for CHIKV infection are of concern. Only one vaccine is available after the U.S. FDA approval in 2023. However, due to its novelty, vaccination remains extremely limited in accessibility and availability, especially for endemic countries (Ng et al., 2024). Furthermore, all available treatments for Chikungunya fever are palliative and supportive care to alleviate pain and symptoms (WHO, 2022). The viremia exists for a short period of 2-3 days during acute infection but could exist in the affected joints during chronic infection. With a significant portion of patients debilitated from CCD, the lack of antivirals to address the underlying viral infection poses a global health problem of the reduced quality of life (Battisti et al., 2021). Therefore, the development of Chikungunya antivirals could be beneficial for treating CCD that would greatly impair the quality of life.

Throughout this ongoing antiviral search, many approaches have been considered in determining which mechanism and target may be the most effective. Some have taken the route of blocking the

entry of CHIKV, while others chose to disrupt the process of viral genome replication (Battisti et al., 2021). There are also several drug repurposing trials, in which licensed antivirals or drugs of other diseases such as favipiravir and ribavirin are tested against CHIKV (Hucke & Bugert, 2020).

This study represents a continuation of high-throughput screenings conducted by Chulalongkorn University's Center of Excellence in Applied Medical Virology on novel quinoline derivative compounds for potential Chikungunya antivirals. Within its batch, the compound STK113 passed the cutoff threshold of 80% to maintain cell viability while exerting viral inhibition. Additionally, it showed the best results in the EC50 tests, reducing 50% of CHIKV titers at a low concentration of 1.832 ± 0.188 μM. Due to this, STK113 shows promise as a candidate for further anti-Chikungunya analysis, specifically to characterize its mode of action, first by investigating which stage of the infectious cycle it can act against.

1.2 Objective

The objective of the research is to determine at which stage of the CHIKV infectious cycle the Lapatinib derivative, compound STK113, can exert its antiviral abilities using an *in vitro* approach with Vero cells as a model.

1.3 Hypothesis

The hypothesis for this study is that due to the nature as tyrosine kinase inhibitors of epidermal growth factor receptors (EGFR), the derivative compound may exhibit antiviral activity against CHIKV by blocking EGFR phosphorylation, potentially at the early stages of the viral infectious cycle.