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Antiviral Activity of Synthetic Bis-Naphthoquinone (H-5) Against Chikungunya Virus Replication

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Abstract

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus that has emerged as a major global public health concern due to its rapid spread and the absence of specific antiviral therapies. Infection with CHIKV commonly causes high fever, severe polyarthralgia, myalgia, headache, and skin rash, with joint pain often persisting for months or years, significantly affecting the quality of life of infected individuals. Although supportive care remains the primary treatment option, the growing burden of chikungunya has emphasized the need for the development of safe and effective antiviral agents. Among various compounds investigated, naphthoquinone derivatives have attracted considerable attention because of their broad-spectrum biological activities, including antiviral, antibacterial, antifungal, antiparasitic, anticancer, and anti-inflammatory properties.

Synthetic bis-naphthoquinone (H-5) has recently emerged as a promising antiviral candidate against CHIKV. Experimental studies have demonstrated that H-5 effectively inhibits viral replication in infected cells while exhibiting comparatively low cytotoxicity toward host cells. In addition, preclinical investigations suggest that H-5 can reduce viral load and improve disease outcomes in animal models. The antiviral effect of H-5 is believed to result from interference with critical stages of the viral replication cycle, making it a potential lead molecule for the development of novel anti-chikungunya therapeutics. Furthermore, studies have reported enhanced antiviral activity when H-5 is used in combination with ribavirin, indicating the possibility of combination therapy for improved clinical efficacy.

Keywords: Chikungunya Virus, Synthetic Bis-Naphthoquinone, H-5, Antiviral Activity, Viral Replication, Naphthoquinone Derivatives

1. Introduction

1.1 Overview

Chikungunya virus (CHIKV) is an arthropod-borne virus (arbovirus) transmitted primarily through the bites of infected Aedes aegypti and Aedes albopictus mosquitoes. Since its first identification in Tanzania in 1952, chikungunya has emerged as a significant public health concern in tropical and subtropical regions of the world. Over the past two decades, frequent outbreaks have occurred in Asia, Africa, Europe, and the Americas, affecting millions of people. The increasing geographical spread of

mosquito vectors, climate change, rapid urbanization, international travel, and globalization have contributed to the re-emergence and transmission of CHIKV.

The name "Chikungunya" originates from the Makonde language of East Africa and means "that which bends up," referring to the characteristic stooped posture of infected patients caused by severe joint pain. Although the disease has a relatively low mortality rate, it causes considerable morbidity due to persistent arthritis, prolonged fatigue, and musculoskeletal pain that may continue for several months or even years after the acute infection.

CHIKV belongs to the genus Alphavirus within the family Togaviridae. It is an enveloped, positive-sense single-stranded RNA virus with a genome of approximately 11.8 kb. The viral genome encodes four non-structural proteins (nsP1–nsP4), which are responsible for viral replication, and five structural proteins (capsid, E3, E2, 6K, and E1), which are involved in virus assembly, maturation, and entry into host cells. Viral entry occurs through receptor-mediated endocytosis, followed by fusion of the viral envelope with the host endosomal membrane and release of viral RNA into the cytoplasm. The virus then utilizes the host cellular machinery to synthesize viral proteins, replicate its genome, assemble progeny virions, and release them to infect neighboring cells.

1.2 Clinical Importance

The incubation period of chikungunya infection generally ranges from 2–7 days. Patients commonly present with sudden-onset high fever, severe polyarthralgia, myalgia, headache, fatigue, nausea, and maculopapular skin rash. The hallmark feature of the disease is debilitating bilateral joint pain involving the wrists, ankles, knees, fingers, and small joints. While most patients recover within a few weeks, a substantial proportion experience chronic arthritis and recurrent joint pain lasting months or years. Elderly individuals, neonates, and patients with preexisting medical conditions are at greater risk of severe disease and complications.

Currently, there is no specific antiviral drug approved for the treatment of chikungunya virus infection. Patient management is largely supportive and includes adequate hydration, rest, analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs) after dengue infection has been excluded. Although vaccine development has advanced considerably, access remains limited in many regions, and there is still a need for effective antiviral agents capable of reducing viral replication and disease severity.

1.3 Need for Novel Antiviral Agents

The absence of licensed antiviral drugs has encouraged researchers to investigate natural products, synthetic compounds, and repurposed drugs for anti-CHIKV activity. Several classes of molecules, including flavonoids, alkaloids, nucleoside analogues, coumarins, quinones, and heterocyclic compounds, have demonstrated antiviral effects in experimental studies. However, many candidates exhibit limitations such as poor bioavailability, toxicity, inadequate selectivity, or insufficient efficacy in animal models and clinical settings.

Among these compounds, naphthoquinone derivatives have attracted considerable interest because of their broad spectrum of biological activities. These molecules possess antiviral, antibacterial, antifungal, antiparasitic, anti-inflammatory, and anticancer properties. Structural modifications of the naphthoquinone scaffold have led to the development of synthetic derivatives with enhanced pharmacological activity and reduced toxicity. Their ability to interfere with viral replication, modulate oxidative stress, and influence host-cell signaling pathways makes them attractive candidates for antiviral drug development.

1.4 Synthetic Bis-Naphthoquinone (H-5)

Synthetic bis-naphthoquinone (H-5) is a newly investigated synthetic derivative that has shown promising antiviral activity against chikungunya virus. Recent experimental studies have demonstrated that H-5 significantly inhibits viral replication in infected cells while maintaining comparatively low cytotoxicity toward host cells. In animal models, H-5 has been associated with reduced viral load and improved survival. In addition, combination therapy with ribavirin has shown enhanced antiviral efficacy, suggesting that H-5 may act synergistically with existing antiviral agents.

Although research on H-5 is still in its early stages, the available evidence indicates that this compound has the potential to become a lead molecule for future anti-chikungunya drug development. Further studies are required to elucidate its molecular targets, optimize its pharmacokinetic properties, evaluate long-term safety, and establish clinical efficacy.

1.5 Aim of the Review

The aim of this review is to summarize and critically discuss the available scientific evidence regarding the antiviral activity of synthetic bis-naphthoquinone (H-5) against chikungunya virus replication. The review highlights the epidemiology, virology, and pathogenesis of CHIKV, explores the pharmacological significance of naphthoquinone derivatives, examines the mechanism of action and experimental findings of H-5, compares it with other antiviral candidates, and identifies current research gaps and future directions for the development of effective anti-CHIKV therapeutics.

2. Preclinical Evidence for the Antiviral Activity of H-5

Experimental and preclinical studies have evaluated the antiviral activity of synthetic bis-naphthoquinone (H-5) against CHIKV using both in vitro and in vivo models. In vitro assays in Vero cells have demonstrated a significant, dose-dependent reduction in viral RNA levels and viral titre following H-5 treatment, alongside low cytotoxicity toward host cells, reflected in a favourable selectivity index. In vivo studies in mouse models have similarly reported a significant reduction in serum viral load and improved survival relative to untreated controls. Combination treatment with H-5 and ribavirin has produced a synergistic antiviral effect, suggesting that H-5 may complement existing broad-spectrum antivirals rather than act only as a standalone agent. These findings are summarized in Table 2.

Table 2: Summary of Preclinical Antiviral Effects of H-5 Against CHIKV

Model	Parameter Assessed	Reported Effect of H-5	Reference
In vitro (Vero cells)	Viral RNA (qRT-PCR)	Significant reduction in viral RNA	Kadam et al., 2017
In vitro (Vero cells)	Viral titre (PFU assay)	Dose-dependent reduction in viral titre	Kadam et al., 2017
In vitro	Cytotoxicity (MTT assay)	Low cytotoxicity; selectivity index > 10	Kadam et al., 2017
In vivo (mouse model)	Viral load in serum	Significant reduction	Kadam et al., 2017
In vivo (mouse model)	Survival rate	Increased survival compared to control	Kadam et al., 2017
Combination	H-5 + ribavirin	Synergistic antiviral effect	Kadam et al.,

therapy			2017

Note: Data compiled from the source study (Kadam et al., 2017) as reported in the H-5/CHIKV literature summarized in this review. Authors should verify and complete the full citation for this source before submission.

3. Chikungunya Virus Replication Cycle

The replication cycle of chikungunya virus (CHIKV) occurs entirely in the cytoplasm of the infected host cell and involves a series of coordinated events that enable viral multiplication. Initially, the virus attaches to specific receptors on the host cell surface through the E2 envelope glycoprotein. The virus then enters the cell by receptor-mediated endocytosis. Acidification of the endosome triggers conformational changes in the E1 glycoprotein, resulting in fusion of the viral envelope with the endosomal membrane and release of the positive-sense single-stranded RNA genome into the cytoplasm. The released viral RNA functions directly as messenger RNA (mRNA) and is translated to produce the non-structural proteins (nsP1, nsP2, nsP3, and nsP4). These proteins assemble to form the viral replication complex, which synthesizes a complementary negative-strand RNA intermediate. This intermediate serves as a template for the production of new genomic RNA molecules and subgenomic RNA.

The subgenomic RNA is translated into structural proteins, including the capsid protein and the envelope glycoproteins (E3, E2, 6K, and E1). The capsid protein encapsidates the newly synthesized genomic RNA to form nucleocapsids, while the envelope glycoproteins are processed through the endoplasmic reticulum and Golgi apparatus before being transported to the plasma membrane. Finally, mature virions assemble at the cell membrane and are released by budding, enabling infection of neighboring cells. Synthetic bis-naphthoquinone (H-5) is reported to act at the RNA replication stage of this cycle, thereby limiting downstream structural protein synthesis, virion assembly, and the release of progeny virus (Figure 1).

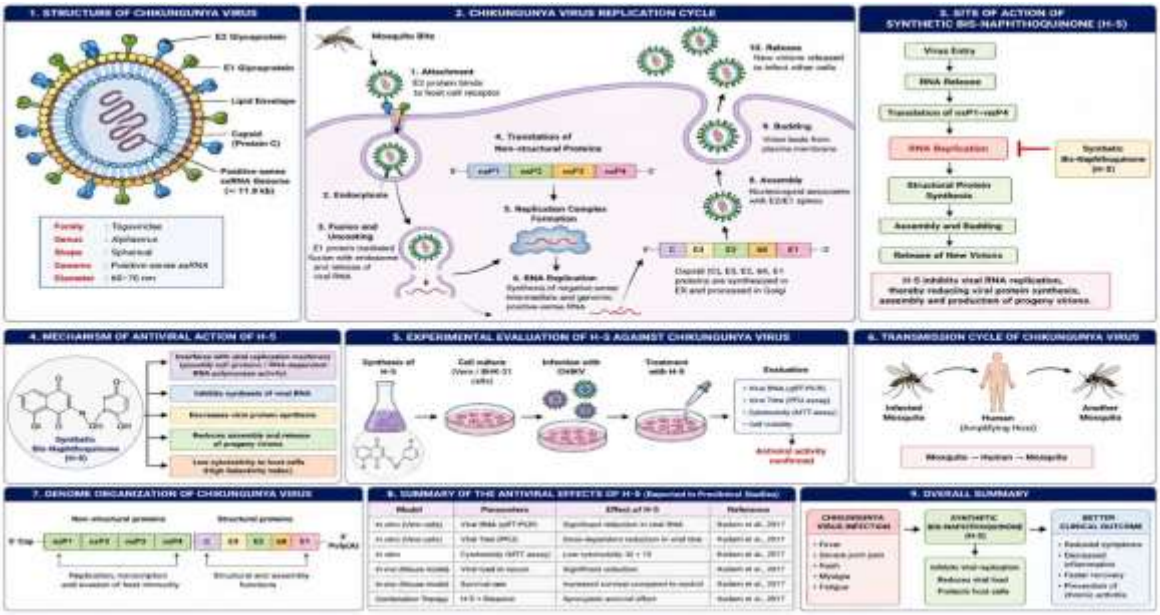

Figure 1: Structure, Replication Cycle, and Site of Antiviral Action of Synthetic Bis-Naphthoquinone (H-5) Against Chikungunya Virus

Table 1: Summary of the Chikungunya Virus Replication Cycle

Step	Viral Event	Major Viral Proteins
1	Attachment to host cell	E2
2	Endocytosis	E1, E2
3	Fusion and uncoating	E1
4	Release of viral RNA	Viral genome (positive-sense ssRNA)
5	Translation of non-structural proteins	nsP1, nsP2, nsP3, nsP4
6	Viral RNA replication	Replication complex (nsP1–nsP4)
7	Structural protein synthesis	Capsid, E3, E2, 6K, E1
8	Assembly of virions	Capsid
9	Budding and release	Envelope proteins (E1 and E2)

4. Clinical Management and Interprofessional Care

Chikungunya fever is a mosquito-borne viral illness caused by CHIKV and transmitted primarily by Aedes mosquitoes. It typically presents with an acute febrile illness characterized by severe polyarthralgia, rash, and fatigue, with joint symptoms that may persist for months to years in some patients. Although mortality is low, the disease can cause significant morbidity, particularly in older adults and those with underlying medical conditions. Diagnosis is based on clinical presentation and confirmed with molecular or serologic testing, while management remains largely supportive, focusing on symptom control and prevention of complications.

Effective management of chikungunya fever requires coordinated interprofessional care to optimize patient outcomes and safety. Physicians and advanced practitioners play a central role in diagnosis, risk stratification, and management planning, including distinguishing CHIKV infection from other arboviral illnesses. Nurses contribute through patient monitoring, symptom management, and education on hydration, medication use, and vector prevention strategies. Pharmacists support safe and appropriate medication selection, particularly in avoiding NSAIDs until dengue has been excluded, and assisting with the management of chronic arthralgia. Collaboration with specialists in rheumatology and ophthalmology may be necessary for patients with persistent or complicated disease. Clear communication among team members and with public health authorities enhances surveillance, outbreak response, and patient education, ultimately improving patient-centered care, reducing complications, and strengthening overall healthcare team performance.

5. Comparison with Other Antiviral Agents Investigated Against CHIKV

H-5 is one of several classes of compounds that have been investigated for anti-CHIKV activity, alongside natural products, other synthetic small molecules, repurposed broad-spectrum antivirals, and host-targeting or nucleoside-analogue agents. Table 3 summarizes representative examples reported in the literature, and Figure 2 places H-5 within this broader classification, highlighting its proposed site of action at the RNA replication step relative to other mechanisms described for these agents.

Table 3: Representative Antiviral Agents Investigated Against Chikungunya Virus

Compound / Class	Reported Mechanism or Target	Reference(s)
Suramin	Interacts with virions; blocks early steps of infection / entry	18, 19, 38

Arbidol	In vitro antiviral activity; resistant mutants characterized	20
Selected flavonoids	Antiviral activity; computational target prediction	21, 36
β-D-N4-hydroxycytidine (NHC)	Nucleoside analogue; induces lethal mutagenesis of viral genome	23, 24
Favipiravir (T-705)	Broad-spectrum antiviral; resistance mutations mapped in nsPs	25, 26
Furin inhibitors	Impair maturation of the E2 surface glycoprotein	27
Host OAS3	Host restriction factor with antiviral effect against CHIKV	28
Naphthoquinone sulfonamide/sulfonate esters	Synthetic naphthoquinone derivatives with anti-CHIKV activity	29
Bis-naphthoquinones (related to H-5)	Reported inhibition of Zika virus replication	30
Radicicol	Targets non-structural protein 2 (nsP2)	37
Nobiletin	In vitro antiviral activity against CHIKV	41
Synthetic bis-naphthoquinone (H-5)	Inhibits viral RNA replication; low host cytotoxicity; synergy with ribavirin	31

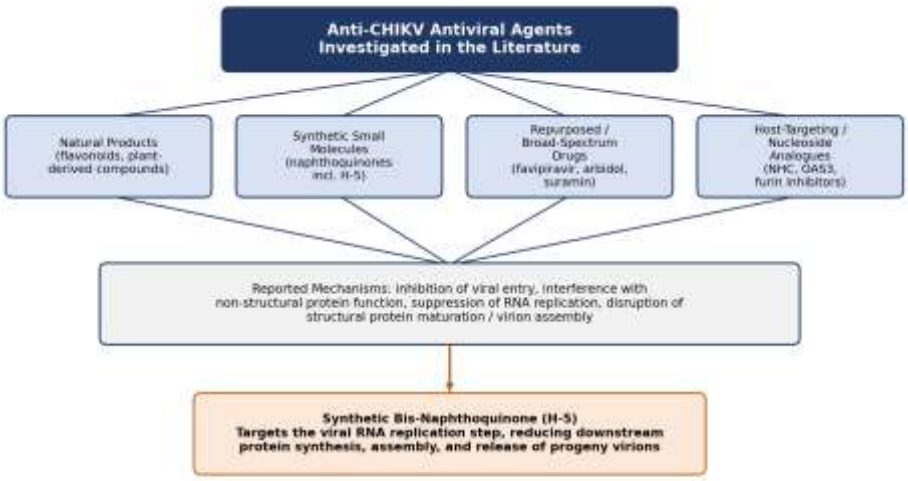

Figure 2: Classification of Antiviral Agents Investigated Against Chikungunya Virus, Highlighting the Proposed Site of Action of H-5

6. Conclusion

Chikungunya virus (CHIKV) is an important mosquito-borne pathogen that causes severe fever and debilitating joint pain. The absence of widely available specific antiviral therapy highlights the need for novel anti-CHIKV agents. Naphthoquinone derivatives have attracted attention because of their diverse

biological and antiviral activities. Synthetic bis-naphthoquinone (H-5) has shown promising antiviral activity against CHIKV. Experimental findings indicate that H-5 can inhibit viral replication with comparatively low cytotoxicity. H-5 has also demonstrated beneficial antiviral effects in preclinical models. Its enhanced activity in combination with ribavirin suggests potential for combination therapy. The CHIKV replication cycle provides several possible targets for antiviral intervention. H-5 may interfere with critical stages of viral replication, reducing viral production. However, its precise molecular mechanism and therapeutic potential require further investigation. Future studies should evaluate its pharmacokinetics, safety, mechanism of action, and clinical efficacy. Overall, H-5 represents a promising lead compound for the development of novel anti-chikungunya therapeutics.

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