

## I. INTRODUCTION

### 1.1 Background Information

To put light on the burden of skin disease on the global map, it is important to note that skin disease is ranked as the fourth most common cause of all human diseases in the world (Flohr & Hay, 2021). Among them, psoriasis is the most prevalent chronic inflammatory skin disease, impacting 2-3% of the global population, with an increasing trend over the last three decades (AlQassimi et al., 2020). Cutaneous psoriasis is clinically characterized by the manifestation of scaly erythematous eruption in the skin epidermal associated with keratinocyte hyperproliferation and inflammation in the epidermis and dermis (Chang et al., 2023). It is an intricate, multifaceted disorder where the interplay of genetic and environmental factors contribute to its development. Environmental triggers, such as stress and infections, can interact with genetic susceptibility to initiate or exacerbate psoriasis. It is known that the pathogenesis is primarily caused by the interaction of immune cells and keratinocytes that induces inflammatory skin response (Rendon & Schäkel, 2019). Aside from cutaneous manifestations, psoriasis can induce systemic illness and disability due to the circulation of inflammatory cytokines in the whole body (Tashiro & Sawada, 2022). Furthermore, its morbidity is also associated with psychological stress in some patients (Snast et al., 2018). Ironically, the burden of this disease is often underestimated despite the high morbidity affecting the largest organ in the body, the skin. Psoriasis goes beyond aesthetic challenges by causing persistent itching, pain, bleeding, discomfort, and functional limitations. These factors do not just affect the visible symptoms but significantly impact patients' daily lives, contributing to an elevated burden of the disease (Oliver et al., 2010).

Despite strides in drug discovery, achieving a satisfactory outcome in developing effective treatments for psoriasis remains a challenge. Psoriasis currently has no cure and existing treatments primarily center on symptom management to improve the well-being of patients. Moreover, the current first-in-line topical therapies for psoriasis are costly and ineffective due to the high possibility of relapse and several adverse effects ranging from mild skin irritation to carcinogenic immunosuppression (Kerdel & Zaiac, 2015). With that being said, the discovery of novel compounds with anti-inflammatory properties is urgently needed to develop inexpensive yet effective treatments with minimal adverse effects to improve treatment outcomes subsequently. For the past few years, substantial efforts have been dedicated to exploring novel anti-inflammatory agents (Brahmachari, 2019). Based on prior research, it has been noted that compounds featuring the naphtho[1,2-d]imidazole skeleton exhibit anti-inflammatory effects by effectively inhibiting the synthesis of nitric oxide (NO) and prostaglandin E2 (PGE2) as a pro-inflammatory molecule (Bian et

al., 2001). Building upon this foundation, this study sought to enhance the anti-inflammatory properties with continuous structural modifications, such as incorporating other scaffolds. For instance, a 1,2,3-triazole structure – a heterocyclic scaffold of significant prevalence in medicinal chemistry – is readily attainable through "click chemistry" methodologies and demonstrates stability under various conditions (Tseng et al., 2009). Considering this, the current focus is to investigate whether compounds possessing a similar structural framework can inhibit the expression of inflammatory cytokines. The said compounds can then be subjected to the development of skin inflammation treatment (mainly focusing on psoriasis). Within this context, there are 13 synthetic compounds with slight structural modification to be examined, namely CCL-7017q, CCL-7018r, CCL-7021u, CCL-7023w, CCL-7025y, CCL-7027a, CCL-7029c, CCL-7030d, CCL-7031e, CCL-7033g, CCL-7036j, CCL-7037k, and CCL-7040n.

### **1.2 Objective**

The main objective of this project was to discover potential compounds by inspecting the anti-inflammatory potential and cytotoxic activity of 13 synthetic compounds using macrophages as the cell model.

### **1.3 Hypothesis**

It was hypothesized that these compounds have the ability to inhibit the expression of inflammatory cytokines and, therefore, would be suitable as potential drug candidates.