Introduction

Over time, there have been various ways to reduce the prevalence of diseases caused by bacteria (including bacterial infections), and in a medical point of view, antibiotics have been long considered as the "standard stock" for curbing pathogenic bacteria. Over the years however, the rise of multi-drug resistant bacterial strains has posed novel challenges in the control of bacterial diseases, which not only translates to enhanced morbidity and mortality, but also translates to an increase in healthcare expenses due to the replacement of old drugs with novel ones (Tanwar, Das, Fatima, & Hameed, 2014).

One has been highlighted of many biochemical pathways utilised by bacteria as a possible novel target of inhibition by antibiotics. In developing such compounds, one viable strategy is to look for a biochemical pathway absent in the host organism to prevent adverse effects on the organism mentioned above when one of the enzymes participating in the pathway is inhibited. The shikimate pathway, present in microorganisms and plants but never animals, and serving as the precursor to the aromatic amino acids, vitamins E and K, folic acid, ubiquinone, plastoquinone, and siderophores crucial for bacterial growth (Herrmann & Weaver, 1999; Hoch & Nester, 1973; Bentley & Haslam, 1990; Řezanka, Palyzová, Faltýsková, & Sigler, 2019), is an example. So far, only one shikimate pathway-targeting compound, N-phosphonomethylglycine, an inhibitor of 5-enolpyruvate shikimate-3-phosphate synthase, has been put into commercial use (Cheung et al, 2014).

An enzyme participating in the shikimate pathway, 3-dehydroquinase, also known as 3-dehydroquinate dehydratase (EC 4.2.1.10), converts 3-dehydroquinate (**1**; **Figure 1**) giving 3-dehydroshikimate (**2**; **Figure 1**), and initiates the aromatisation process in the pathway. 3-dehydroquinase comprises two structurally unrelated types (types I and II); the Type I variety carries

out a cis-dehydration of 3-dehydroquinate via a covalent imine intermediate, exists as a heat-labile homodimer and only participates in the biosynthetic (shikimate) pathway; of interest, González-Bello (2015) noted the suggestion of type I 3-dehydroquinase acting as a bacterial virulence factor *in vivo*, adding that the deletion of the aroD gene encoding the enzyme had been proven to afford satisfactory live oral vaccines against *S. typhi* and *Shigella flexneri*. In contrast, the Type II variety catalyses a trans-dehydration of its substrate via an enolate intermediate, exists as a heat-stable dodecamer and plays a role in both biosynthetic and catabolic (quinate) pathways; the latter involves the utilisation of quinate as a carbon source for procathechuate synthesis (Dev, Tapas, Pratap, & Kumar, 2012; Dias et al, 2011; Gourley et al, 1999). Pathogenic bacteria known to house type I 3-dehydroquinase include *Escherichia coli*, *Salmonella enterica*, and *Clostridium difficile* (reclassified as *Clostridioides difficile* (Oren & Rupnik, 2018)); on the other hand, bacteria such as *Mycobacterium tuberculosis*, *Streptomyces coelicolor* and *Helicobacter pylori* utilise the Type II variety (Cheung et al, 2014; Dev, Tapas, Pratap, & Kumar, 2012; Dias et al, 2011).

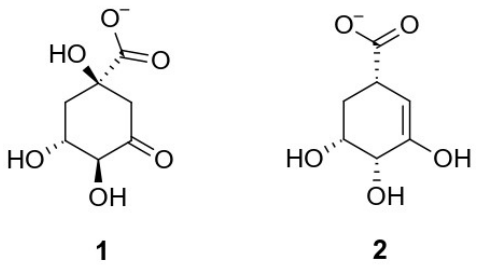

*Figure 1. Skeletal structures of 3-dehydroquinate (**1**) and 3-dehydroshikimate (**2**).*

As one of the most widely utilised sources of currently-used antibiotics, the Gram-positive, filamentous, spore-forming bacterial genus *Streptomyces* (Chang & Cohen, 1994) first attracted attention when one of the compounds produced by one species of *Streptomyces* (*S. griseus*) named streptomycin was highlighted as a promising compound in a drive to find novel antibiotics effective

against tuberculosis; since then, with the increased incidence of multi-drug resistant pathogenic bacterial strains and shortage of available medications, the quest to discover novel *Streptomyces*-produced compounds may bring about a new generation of antibiotics (Quinn, Banat, Abdelhameed, & Banat, 2020). The antibiotics themselves, with differing molecular structures and weights, are not limited to their antibacterial activity but some also exhibit antifungal and antineoplastic activity, to name a few.

Drug discovery encompasses two main approaches, one relying on the pharmacophores of ligands and their structure-activity relationships to modify the functional groups of active compounds (ligand-based drug discovery/LBDD) and the other requiring knowledge about the target macromolecule and its active site conveyed as its three-dimensional (3D) structural representation (structure-based drug discovery/SBDD); the latter mainly involves an approach known as molecular docking, a computational method of finding the most suitable interaction patterns between two molecules known as a "receptor" and a "ligand", and a real proof of how computers can participate in designing novel drug candidates in a process known as computer-aided drug design (Tim Inbio Indonesia, n.d.; Widodo, Utomo, Ramadhani, Hasanah, & Fitriah, 2018).

The current work involved, as a main objective, the docking of a model of type I 3-dehydroquinase with a selected collection of potentially orally bioavailable *Streptomyces*-produced compounds in search of promising "hit" compounds, assuming that the compounds were intended for oral administration. As for the choice of the target macromolecule, the type I variety was the one that was utilised by most bacteria and higher plants (Herrmann, 1995). It was expected that only certain docked compounds possess favourable macromolecule-ligand binding affinities.