**4.B.6 Trans-Sialidase’s Role in Chronic Chagas Disease, and its Potential for Infection Inhibition by Employing Natural Products**

Currently there are 8 to 10 million people worldwide infected by Chagas Disease, a parasitic infection caused by the protozoan Trypanosoma Cruzi (T. Cruzi). The vast majority of infected individuals live in rural areas of Latin America with limited healthcare access. If untreated they will suffer from a lifelong infection, which could ultimately lead to severe cardiac muscle and gastrointestinal damage and eventually result in death. The malady can be successfully treated in the acute phase; however, this phase often goes unnoticed. Once the malady enters the chronic phase (about 90 days after infection) there are no good drugs to treat it. The available drugs, which are administered in both the acute and chronic phases, can cause severe negative side effects and have limited efficiency in eliminating the parasite from the host, especially once the disease has entered the chronic phase. Accordingly, there has been a growing interest in developing drugs that target the protozoan directly on a biochemical level.

Several novel drug targets have been suggested, and among those is the surface protein, Trans-sialidase (TcTS), found on the membrane of the protozoan. This protein promotes host cell invasion, and allows the parasite to evade cell defenses, such as lytic processes. Furthermore, it has been suggested that it might play a role in immunomodulation, which permits the protozoan to elude immune responses and live in the host for decades, allowing it to become a chronic infection. Thus, TcTS has an important role for T. Cruzi’s survival success.

An in-silico approach was utilized for this study, since the protein structure of TcTS had already been identified. The structure was docked, using both AutoDock Vina and AutoDock 4.2, to compounds in the Taiwan Pharmaceutical Database (http://tpd.mc.ntu.edu.tw/index.php), where several candidates were identified. *Dihalenaquinolide A*, derived from a Taiwanese marine sponge, *petrosia elastic* (Figure 1), had (among all screened natural products) a consistent high binding affinity at around -15.2 kcal/mol to TcTS’s active site. Moreover, by running a perl script, it was determined that key residue interactions, such as Asp59 (which is essential for catalysis), were established between the two species. Other noteworthy compounds with consistently promising results were, *(+)-Ovigeridimerin*, derived from the trunk bark of *hernandia nymphaeifolia*, with -13.5 kcal/mol; and *Bisisodiospyrin*, identified in the stem of *diospyros maritime*, with -15.7 kcal/mol.

Chagas Disease is a malady affecting a highly vulnerable population and great efforts have been made globally to find a cure. Some potential drug candidates have been synthetic, but more often natural products have shown to be good templates and are novel in their drug design. The identified candidates, however, are just the first step in a long process in determining their actual efficiency as an inhibitor to TcTS processes. Ultimately, in-vitro assays will have to be performed to verify the in-silico predictions.

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Figure 1: *Dihalenaquinolide A* docked to Trans-sialidase (PDB ID: 1M08)