Design and Optimization of *Toxoplasma gondii* Cathepsin Protease L (TgCPL) Inhibitors for the

Treatment of Toxoplasmosis

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Toxoplasmosis, an infection caused by the intracellular protozoan parasite *Toxoplasma gondii* (*T. gondii*), is one of the most prevalent infections with an estimated 2 billion people infected worldwide. Additionally, *T. gondii* infection is one of the leading causes of death due to foodborne illness in the United States. While infection is generally asymptomatic in immunocompetent patients, *T. gondii* poses significant health risks in immunocompromised and pregnant patients including central nervous system (CNS) disorders, vision loss, and fetal complications. Growing evidence had revealed that *T. gondii* infection has an association with mental illnesses including anxiety and depression. Once infected with *T. gondii*, the infection will persist lifelong in the patient in the form of cysts within the CNS, muscle, and ocular tissue that can reactivate into an acute infection if the patient becomes immunocompromised.

Therapies are available to treat reactivation of *T. gondii*, however, these agents are unable to treat and clear the latent infection. Moreover, these agents suffer from potentially serious adverse events and contraindications that limit their use to certain patient populations. *T. gondii* cathepsin L (TgCPL) has emerged as a promising drug target for the treatment of latent toxoplasmosis due to its critical role in the life cycle of the parasite. In this project, triazine nitrile TgCPL inhibitors were discovered, and initial optimization efforts were conducted to improve their potency towards TgCPL. Through rational design, nanomolar potency was achieved in this series and pharmacophore features were identified that could be further exploited to achieve selectivity for TgCPL over human cathepsin L (HsCPL). Current work will further expand upon previous efforts to optimize the triazine series through chemical synthesis efforts. These efforts are aimed to address gaps in the current structure activity relationship (SAR) and lead to the development of inhibitors in these series with optimized potency, selectivity, and pharmacokinetic (PK) properties including microsomal stability and permeability.