Determination of the *in vitro* effectiveness of novel Tipifarnib analogs via a fluorescence-based assay

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Protein prenylation is a post-translational modification where a C-15 or C-20 isoprenoid is appended to the C terminal end of a protein by either farnesyltransferase or geranylgeranyl transferase type 1, respectively. The isoprenoids are attached to the Cysteine residue of a four amino acid CaaX box sequence. Prenylated proteins have been implicated in many diseases, with the most infamous example being the mislocalization of RAS in cancer. In addition, changes in the expression of certain prenylated proteins has been shown to be important in many other illnesses including ALS, Alzheimer’s Disease, and malaria. Recently, our lab has made analogs of the well-known farnesyltransferase inhibitor Tipifarnib, with the goal of gaining selectivity for the farnesyltransferase of pathogenic organisms including yeast and plasmodium falciparum. The IC50 values of these compounds can be assayed using a fluorescence based assay utilizing a substrate peptide with a fluorescent Dansyl functional group. This fluorophore is extremely sensitive to the environment, and the fluorescence intensity greatly increases when the substrate peptide is prenylated. Some of these compounds show high selectivity for the plasmodium farnesyltransferase enzyme and are promising potential drug candidates.