ABSTRACT

Tankyrase 1 has received attention as a promising target for anti-cancer therapies due to its upregulated expression in various cancer types. Its crucial role in PARsylation leads to the degradation of tumor suppressors (e.g. Axin, TRF1, and PTEN) through the ubiquitin-proteasome pathway, highlighting its significance in oncogenic processes. The urgency to discover novel tankyrase 1 inhibitors stems from concerns about potential off-target effects associated with existing inhibitors. Notably, there is currently no tankyrase 1 inhibitor in clinical use with a limited number of compounds are undergoing clinical trials. This study addressed this gap by identifying new potential tankyrase 1 inhibitors using a humanized yeast cell-based bioassay. It was found that both *PPΔ* and *EPPΔ* strains were deemed unsuitable and not functional for use in the screening system due to persistent drug resistance and the loss of the tankyrase 1 toxicity phenotype, respectively. Despite facing challenges with the screening system, compounds namely N20, N648, N661, and S73 exhibited growth rescue in yeast cells upon tankyrase 1 inhibition during the initial screening (conducted before the internship). Subsequent testing in the MTT assay for cancer cell viability highlighted N661 as the most potent inhibitor, followed by N648, which demonstrated a dose-dependent decrease in cancer cell viability. These findings suggest the promising potential of N661 and N648 as tankyrase 1 inhibitors, opening opportunities for the advancement of targeted therapies specifically designed for cases of tankyrase 1 overexpression.

Keywords: tankyrase 1, cancer, PARsylation, yeast cell-based screening system, tankyrase 1 inhibitor, *S. cerevisiae*