ABSTRACT

Glioblastoma multiforme (GBM) is the most lethal primary brain malignancy in adults, with a median overall survival of 12–15 months despite maximal therapy. Resistance to the standard chemotherapeutic agent temozolomide (TMZ) remains a near-universal clinical obstacle, motivating the development of mechanistically distinct therapeutic strategies. ORAI1-mediated store-operated calcium entry (SOCE) is aberrantly elevated in GBM and drives pro-survival AKT signaling, including MDM2-dependent suppression of the tumor suppressor p53, representing a tractable but underexplored therapeutic target. Although the parent ORAI1 inhibitor Synta66 efficiently suppresses SOCE, previous studies demonstrated minimal or absent cytotoxic and anti-proliferative activity in GBM cell lines, limiting its therapeutic applicability as a standalone anti-cancer agent. Hence, a structurally modified derivative library was developed to improve the cytotoxic efficacy of Synta66 while retaining ORAI1-targeting activity. Twenty structural derivatives of the ORAI1 inhibitor Synta66 (MPT1B783–MPT1B802) were screened at 10 µM against A172 GBM cells using the MTT cytotoxicity assay at 24 and 72 hours. MPT786 demonstrated the most pronounced reduction in cell viability (69.7 ± 9.2% at 24 hours; 53.6 ± 11.4% at 72 hours) and was selected for dose-response characterization, yielding an IC_{50} of 9.020 µM (95% CI: 7.977–10.44 µM; R^2 = 0.9287) in A172 cells. Time-dependent cytotoxicity assays across four GBM cell lines: A172, A172-R, U-87 MG, and U-87 MG-R, which are confirmed to be statistically significant and sustained anti-proliferative activity in all models, including TMZ-resistant derivatives (A172-R and U-87 MG-R), suggesting that MPT786 activity may not be substantially impaired by O^6-methylguanine-DNA methyltransferase (MGMT)-associated resistance mechanisms. These findings identify MPT786 as a lead ORAI1 inhibitor derivative warranting mechanistic validation and structural optimization for GBM therapeutic development.

Keywords: glioblastoma multiforme, ORAI1, store-operated calcium entry, MPT786, Synta66 derivatives, cytotoxicity, temozolomide resistance