ABSTRACT

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Glioblastoma multiforme (GBM) is the most aggressive type of malignant brain tumour. Despite the multimodality of the treatment options, the survival time is on average 12 to 16 months after diagnosis. The resistance to standard chemotherapy treatment (temozolomide) is mostly caused by the activation of DNA damage response pathways. The main responders are kinases belonging to the phosphatidylinositol 3-kinase-related protein kinases family: ATM (ataxia-telangiectasia mutated), ATR (ATM and Rad3-related), and DNA-PKcs (DNA-dependent protein kinase catalytic subunit). ATR kinase is activated in response to replication stress, and its essentiality for cancer cells is irreplaceable. Therefore, the inhibition of ATR kinase has the potential to sensitise cancer cells to temozolomide and overcome cancer resistance, in general. Some ATR inhibitors have already entered phases II and III of clinical trials. Based on their common structural features, we have designed and synthesised 45 new compounds that were expected to be effective either alone or in combination with chemotherapy. I was involved in synthesising 14 of these compounds. Highlighted molecules have been proven to be effective on GBM patients' samples. Of the compounds synthesised, one was similarly effective in TMZ potentiation as the phase III clinical candidate ceralasertib.