Synthesis of novel small molecule inhibitors as radioprotective agents

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Abstract

Radiation therapy (RT) is commonly used as a component of anticancer therapy for a wide range of cancers. At present, it is estimated that half of all cancer patients will receive radiotherapy during the course of their treatment for cancer. The therapeutic activity of ionizing radiation on cancer cells is primarily based on the cell cytotoxicity derived from the inhibitory effects of radiation on vital biochemical processes in cancer cells. Unfortunately, the interaction of radiation with cells during RT can also cause side effects by damaging noncancerous, healthy tissues surrounding the cancer cells. In this regard, targeting the BH3-only Bcl-2 family pro-apoptotic protein known as p53-upregulated mediator of apoptosis (PUMA) had previously been reported to show radioprotective effects. The presented work is focused on the design, synthesis and *in vitro* screening of PUMA drug inhibitors as novel radioprotective agents for radiation anticancer therapy and as radioprotectors or mitigators for situations including radiation accidents or radiation terrorism.

The aim of this work was to design a set of new potential inhibitors of PUMA-like compounds. The compounds were designed based on the structural research of substances with the same or similar effects known from the literature. The data prediction was applied in order to analyze the suitability of use. The selected structures were then synthetically prepared according to the standard synthetic approaches and verified for their identity and purity by NMR and MS.

To investigate anti-proliferative and cytotoxic activities of the prepared small molecule PUMA inhibitors alone, we determined the cytotoxic effect on cell survival using a panel of 9 human cancer cell lines of different tissue origin (Jurkat, MOLT-4, A549, HT-29, PANC-1, A2780, HeLa, MCF-7 and SAOS-2) compared with non-cancerous human lung fibroblasts MRC-5. Single-dose testing of growth inhibition in the screening panel of human cell lines was performed with 10 newly prepared PUMA inhibitors at a concentration of 10 μM. Proliferation of cells was evaluated at the end of 48 h culture with evaluated inhibitors using the WST-1 tetrazolium salt proliferation assay. The measurements showed that treatment with prepared PUMA inhibitors at 10 μM resulted in no significant changes in the cell proliferation compared to 0.1% DMSO sham control exposure.

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