ABSTRACT

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Cancer is one of the leading causes of fatalities worldwide, which is attracting attention of many researchers with desire to develop treatments that selectively target cancerous cells while simultaneously sparing healthy cells. The main overall strategy is to exploit features specific to cancer – the cancer hallmarks. Those are represented, for instance, by genomic instability and aberrant DNA damage response (DDR) pathways. The DDR consists of cascades of kinases and other proteins and messengers, where we highlighted the synthetic lethal interaction between the kinases ATM (ataxia-telangiectasia mutated) and ATR (ATM and Rad3-related). The two are major driving forces in the DDR, where in cancer ATM tends to be mutated and therefore dysfunctional, making the cells‘ viability reliant on ATR. Thus, ATR inhibition makes a particularly attractive strategy for abrogating cancer survival without affecting the healthy cells. Four ATR inhibitors have already entered clinical trials as anticancer agents - VX-970, VX-803, BAY1895344 and AZD6738. Based on their common structural features and several specificities, with particular focus on VX-970 and its developmental precursor VE-821, we have designed and synthesized 15 novel molecules built on 7-azaindole and 2,7-diazaindole core strucures. These were screened for cytotoxicity against nine cancer and one healthy cell line, with several compounds showing a significant inhibition of cancer cell proliferation in single-agent mode. Combinatorial regimen with cisplatin or temozolomide showed only moderate efficacy with an additive effect.