DESIGN AND SYNTHESIS OF NOVEL PYRROLO[2,3-*c*]PYRIDINES WITH POTENT ANTIPROLIFERATIVE ACTIVITY

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Despite the progress made in early diagnosis and start of treatment of cancer, one in four deaths in the developed countries is due to this disease, and the need for the discovery and development of new antitumor agents is urgent. The use of targeted anticancer therapeutic agents has significantly improved the outcome of the anticancer therapy during the past twenty years. The two main types of molecular targeted therapy are monoclonal antibodies and small molecule kinase inhibitors, and both proved to be very effective, with limited toxicity and side effects. As a result, a great number of these derivatives have recently been approved as anticancer agents.

With the aim to discover novel derivatives with potential cytotoxic activity, our research group has previously synthesized a number of nitrogen containing heterocyclic compounds, that exhibited promising in vitro and/or in vivo anticancer activity. In this work, we have designed and synthesized a number of novel suitably substituted pyrrolo[2,3-*c*]pyridine derivatives, using as a lead compound a recently identified by our group hit [1]. For the synthesis of the target derivatives 2-amino-3-nitro-4-methylpyridine was used as the starting material, which was initially converted to the key intermediate 7-chloropyrrolo[2,3-*c*]pyridine and then the appropriate substituents were incorporated. The new derivatives were subsequently evaluated for their potential to inhibit the proliferation of human origin cancer cell lines, with the MTT assay. The evaluation of the cytotoxicity results revealed interesting SARs concerning the effect of the substitution pattern of the novel compounds on the antiproliferative activity. Interestingly, the new derivatives proved to be more effective against the A431 cancer cell line, which expresses abnormally high levels of the epidermal growth factor receptor (EGFR) and contains no functional p53, a potent tumor suppressor gene.

Reference:

[1] S. Dimitrakis et al., Novel Substituted Purine Isosteres: Synthesis, Structure-Activity Relationships and Cytotoxic Activity Evaluation. *Molecules* **2022**, 27(1), 247.