ABSTRACT

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Title of diploma thesis: Novel structures with a potential to inhibit the FLT3 receptor: In vitro evaluation using AML cell lines

Acute myeloid leukemia (AML) is a rapidly progressing hematologic malignancy, characterized by the proliferation and accumulation of immature myeloblasts in the bone marrow and peripheral blood. Despite significant achievements, treatment outcomes remain unsatisfactory. Mutations in the FLT-3 (FMS-like tyrosine kinase 3) gene are detected in up to one-third of patients with newly diagnosed AML, contributing to the poor prognosis of the disease. FLT-3 inhibitors thus represent a new approach to targeted therapy. Although they have only recently been introduced into therapy, resistance to them is already being developed by leukemic cells, often resulting in treatment failure. In this study, we aimed to test 8 newly synthesized compounds as potential FLT-3 inhibitors and to evaluate their possible contribution in overcoming resistance to the clinically used FLT-3 inhibitor gilteritinib. Using the MTT method, the ability of these compounds to induce cell death was tested in the MV4-11 line (carrying the FLT-3 mutation) in comparison to the THP-1 line (lacking the mutation). Based on the initial screening at 1μM and 10 μM concentrations, the 4 most effective substances were selected, followed by determination of their IC50 values. The compound DS-28 was identified as the most effective, inhibiting the proliferation of the MV4-11 cell line with an IC50 value of 0.3070 μM (95 % CI = 0.2779-0.3386 μM), compared to the THP-1 line, in which the IC50 value was 55 times higher. To evaluate the possible antiproliferative activity in resistant cells, the effect of the compounds was compared between the gilteritinib-resistant HL-60 g75 line and the wild-type HL-60 variant. The compound DS-3 showed a similar effect on cellular proliferation in both, the resistant and the sensitive cell line. Surprisingly, an unexpected effect was observed with LG-1871 and can be presumably explained by the excessive activation of mitochondrial enzymes. These results provide interesting motives for further resistance studies and present the promising compound DS-28 as a potential prototype structure for even more effective FLT3 inhibitors.