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SciTechnol

Kow Koon Kee, J Clin Exp Oncol 2018, Volume 7
DOI: 10.4172/2324-9110-C1-009

23rd International Conference on

Cancer Research & Pharmacology

March 26-27, 2018 Edinburgh, Scotland

Synthesis and biological evaluation of new purine-like heterocyclic molecules targeting apoptosis in cancer cell lines

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Chemotherapy remains its position on the frontline of leukemia treatment. Many of the modern anti-leukemic drugs are purine analogues, e.g. Pentostatin, Cladribine and Fludarabine. In our program on the development of new potent anti-proliferative agents selectively targeting leukemic cells, we identified a new type of purine-like compounds possessing the desirable properties. We prepared a representative library of these compounds and preliminary screening identified several potent molecules, including compound MM0018. Its anti-proliferative activity against Jurkat T cells was assessed at wide range of concentrations and three time points (24, 48 and 72 hours). MM0018 demonstrated significant and concentration dependent inhibition of the Jurkat T cell growth with GI50 values of 50.0±0.2 ng/mL, 7.60±0.4 ng/mL and 1.30±0.1 ng/mL ($p<0.05$) at these points, respectively. The effect of the compounds on the cell morphology was studied microscopically using Hoechst fluorescence staining and Acridine Orange and Propidium iodide (AO/Pi) immunohistochemical staining. It was found that Jurkat T cells treated with GI20 and GI50 of MM0018 at two time points (24 and 48 hours) demonstrated hallmarks of apoptosis, such as chromatin condensation, multi-nucleated cells and formation of apoptotic bodies. It showed that this compound activated caspases-dependent apoptosis pathway as apoptosis was inhibited when caspases-inhibitor z-VAD-fmk was added. No effects on the proliferation of lung cancer (A549), nasopharyngeal carcinoma and non-cancerous human lung fibroblast (MRC75) cells were observed when they were treated with MM0018 at concentrations up to 300 ng/mL. Therefore, we can conclude that MM0018, due to its high potency and selectivity, has a potential for the further development as an apoptosis-inducing anti-leukemic agent.

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