DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION ON NOVEL ACRIDINE DERIVATIVES AS TYROSYL DNA PHOSPHODIESTERASE 1 AND/OR 2 INHIBITORS

Maria Karelou*, Keli Agama**, Evgeny Kiselev**, Yves Pommier**, Ioannis K. Kostakis*

*Division of Pharmaceutical Chemistry, Department of Pharmacy Panepistimiopolis-Zografou, Athens, Greece
**Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland 20892-4255, United States

Topoisomerases are enzymes that regulate the topology of DNA, thus allowing its functions to be performed, namely the replication, transcription, and condensation of chromatin. They act by temporarily cutting and re-joining one or both strands of DNA without the help of additional enzymes. Their mechanism of action is based on the formation of intermediate "cleavage complexes" of enzyme-DNA. Under normal conditions the process of re-joining is faster than that of cleavage, which makes "cleavage complexes" transient in the catalytic cycle of topoisomerases. However, these complexes can remain trapped in DNA by topoisomerase inhibitors, leading to irreversible double helix rupture and therefore apoptosis of cancer cells. But in addition to topoisomerase inhibitors in cancer cells, there are various endogenous and exogenous DNA damage to normal cells, which trap "cleavage complexes" thus blocking DNA recombination. Here are the tyrosyl-DNA phosphodiesterases 1,2 whose normal role is to remove the irreversible "cleavage complexes" created by topoisomerase errors and DNA damage. At the same time, however, they remove the permanent "cleavage complexes" that are created by topoisomerase inhibitors in cancer cells, thus neutralizing their action. It is therefore necessary for inhibitors to be found[(1)] . Thus, taking into account the synergistic effect of topoisomerases with Tyrosyl-DNA Phosphodiesterases, as well as the remarkable action of azaacridine derivatives bearing amino-substituted chains at positions 1.4 and methoxy group at position 8, the new ones were designed. In these derivatives for the study of the structure relationships, the length of the chains has been increased as well as the introduction of nitrogen or oxygen atoms. In addition, aliphatic chains have been replaced by cyclic and aromatic ones. Also the methoxy group at position 8, has been replaced by ethoxy, bromine, trifluoromethyl and phenyl substituted group. Finally, derivatives bearing hydrogen at position 8 and a bromine at position 6 of the azaacridine backbone were designed in order to study this position.

1. Pommier Y., Huang SY., Gao R., Das BB., Murai J., Marchand C., Tyrosyl-DNA-phosphodiesterases (TDP1 and TDP2). *DNA Repair (Amst)*, **2014**, 19, 114-29.