DNA and topoisomerases as molecular targets of novel 2-substituted acridone derivatives

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Acridone derivatives have been explored for their broad range of biological activity, including antibacterial, anti-inflammatory, antiparasitic, antiviral, antimalarial, antitubercular, antiallergic, fungicidal and anticancer activities. They have been reported to interact with proven molecular targets in cancer, including topoisomerases 1 and 2, telomerase and protein kinases [Yadav TT et al. (2022) Eur J Med Chem 239, 114527]. Another target of small organic molecules with anticancer activity is DNA because of its crucial role in cell division. In the case of acridine/acridone derivatives, this interaction is well-established and is primarily achieved through intercalation of the azaheterocyclic chromophore between the base pairs of DNA [De Almeida, SMV et al. (2017) Biomed Pharmacother 96, 1538-1556]. The aim of our research was to study the interaction of six novel 2-substituted acridones with calf thymus DNA (ctDNA) and monitor their inhibition activity against topoisomerases (Topo) 1 and 2α. We have employed spectroscopic methods (UV-Vis, fluorescence and circular dichroism) and thermal denaturation studies of ctDNA to elucidate the binding mechanism between the studied derivatives and ctDNA. The inhibition capacity against Topo 1 and 2α was studied through agarose gel electrophoresis using superspiralized and catenated DNA as substrates, respectively. The results of the spectroscopic studies confirmed a non-covalent interaction between ctDNA and the studied derivatives, which seem to preferably bind into the minor groove of the double helix with partial intercalation of the acridone moiety. Five of the studied compounds exhibited considerable inhibitory activity against Topo 1, while two derivatives were effective against Topo 2α as well. Overall, the results have shown that the studied acridone derivatives could represent promising anticancer agents and are suitable for further research. Acknowledgement: This study was supported by VEGA Grant No. 1/0037/22.

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