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Extended Abstract

3,5-Substituted Oxadiazoles as Catalytic Inhibitors of the Human Topoisomerase IIα Molecular Motor †

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Cancer constitutes a group of diseases linked to abnormal cell growth that can potentially spread to other parts of the body and is one of the most common causes of death. A possible approach in its treatment is to halt uncontrolled cell division by inhibiting molecular motors—DNA topoisomerases—that enable topological changes of the DNA molecule during this process [1]. Type II DNA topoisomerases, especially topo IIα, are established anticancer targets with inhibitors divided into two groups. Topoisomerase poisons are firmly established in clinical use and act by stabilising the cleavage complex between topo IIα and DNA. However, the induction of the double stranded brakes of the DNA molecule caused by this group is associated with severe side effects, such as cardiotoxicity and induction of secondary malignancies [2,3]. A second emergent group of catalytic inhibitors attempts to circumvent these challenges and currently embodies four subgroups of mechanistically diverse inhibitors, one of them being compounds that act by prevent binding of the ATP molecule into its binding site [2–4].

Here, we designed, synthesized, and evaluated new derivatives of the 3,5-substituted oxadiazoles that act as catalytic inhibitors of the human topo IIα. Introduction of rigid moieties into the initially available flexible oxadiazoles served to reinforce the interactions with the ATP binding site. Selected compounds also displayed promising in vitro cytotoxicity properties on the investigated MCF-7 cancer cell line. The predicted inhibitor binding geometries were evaluated in classical molecular dynamic simulations, and structure-based dynophore modes were subsequently derived to provide a deeper insight into the molecular recognition of this class of compounds with its macromolecular target.

References

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