

significant threats to human health. A major challenge in these scenarios is mitigating radiation-induced damage to healthy tissues, driving the need to develop effective radioprotective agents. This study focuses on the design, synthesis, and evaluation of novel piperazine derivatives as potential radioprotective agents to overcome the limitations of current countermeasures. A series of 1-(2-hydroxyethyl)piperazine derivatives was synthesized and their cytotoxicity tested for in various human cell lines. Their radioprotective properties were further assessed in the MOLT-4 lymphoblastic leukemia cell line and peripheral blood mononuclear cells (PBMCs) exposed to gamma radiation. To quantify their ability to reduce DNA damage, the dicentric chromosome assay (DCA) and apoptosis detection were employed. Among the synthesized compounds, compound 6 demonstrated the most potent radioprotective effects *in vitro*, with minimal cytotoxicity. Compound 3 also exhibited notable efficacy, particularly in reducing dicentric chromosomes, suggesting its potential in mitigating DNA damage. Both compounds showed enhanced safety and effectiveness compared to amifostine, highlighting their promise as improved radioprotective agents. Based on the obtained findings, the mentioned compounds served as molecular templates for the synthesis of a new series of substances which show enhanced radioprotective properties. Acknowledgements: This work was supported by grant project NU23-08-00256 of the Ministry of Health.

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Unlocking PD-1/PD-L1 axis in non-small cell lung cancer: *in silico* design of tetrahydroquinoline-based small-molecule immune checkpoint inhibitors

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The programmed cell death protein-1 (PD-1)/PD-L1 immune checkpoint axis is a critical therapeutic target in non-small cell lung cancer (NSCLC); however, treatment resistance and high costs continue to limit the effectiveness and accessibility of current therapies. Development of small-molecule inhibitors targeting the PD-1/PD-L1 interaction offers a promising approach to enhancing efficacy and accessibility. Tetrahydroquinoline (THQ) derivatives, known for their immunomodulatory and apoptosis-inducing effects, have emerged as compelling candidates for dual checkpoint inhibition due to their broad biological activity and role in modulating key cellular processes, making them an attractive scaffold for anticancer drug development. This study employs a structure-based drug design approach to develop novel THQ-based PD-1/PD-L1 inhibitors. Molecular docking (Schrödinger 2020-3, Glide XP) and MM-GBSA calculations identified five leads with superior ΔG_{bind} values ranging from (PD-L1: -28.04 to -49.82 kcal/mol; PD-1: -3.08 to -46.11 kcal/mol), significantly outperforming BMS-200 (ΔG_{bind} = -2.42 for PD-1; -7.54 for

PD-L1). Key interactions involve hydrogen bonding with PD-L1's Lys124 and hydrophobic contacts near Tyr56, alongside analogous interactions with PD-1, reinforcing the dual affinity of THQ derivatives. Guided by these computational insights, chemical synthesis of selected THQ derivatives is currently in progress using optimized synthetic methodologies. To further assess their therapeutic potential, future studies will focus on ADME profiling, molecular dynamics simulations, kinetic and thermodynamic evaluations of PD-1/PD-L1 inhibition, and *in vitro* validation of lead compounds in NSCLC cells (A549). This work aims to advance the development of next-generation small-molecule immune checkpoint inhibitors, bridging the gap between computational drug discovery and translational oncology. *The authors marked with an asterisk equally contributed to the work.

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Identification of potent inhibitors of Zika and Dengue viruses proteases from small-molecule compound libraries

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Zika virus (ZIKV) is a flavivirus transmitted by *Aedes* mosquitoes, responsible for outbreaks of Zika fever, a disease that can result in severe neurological complications such as congenital Zika syndrome and Guillain-Barré. Despite its re-emerging potential, there are no approved antivirals or vaccines against the virus. The NS2B-NS3 protease (NS2B-NS3^{pro}) plays a critical role in processing the viral polyprotein and is a promising drug target. Here, we conducted a high-throughput screening (HTS) of 12 000 compounds from three small-molecule libraries (ReFRAME, HGL1, and HGL2) against the recombinant ZIKV NS2B-NS3^{pro}. Eleven compounds inhibited the enzyme by >80% at 10 μM and six exhibited a concentration-dependent effect with IC_{50} values in the micro to submicromolar range. Those compounds were further evaluated against the viral replicon and three showed antiviral activities resulting in selectivity indices up to 5.2. Additionally, differential scanning fluorimetry (DSF) revealed varied thermal stability effects, supporting direct protein-ligand interactions. To assess cross-inhibition potential, the most potent ZIKV protease inhibitors were tested against the NS2B-NS3^{pro} from Dengue virus (DENV) serotypes 1 to 4. Four compounds inhibited DENV1 protease, while Compound 1 was active against all tested serotypes. Our findings provide valuable insights for antiviral drug discovery targeting flavivirus proteases, with Compound 1 emerging as a promising lead for further optimization.