Anti-neuroinflammatory activity of selected 2-pyridone derivatives: *In vitro* and *in silico* study

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Pyridones constitute a significant class of heterocyclic compounds that are prevalent within natural compounds and synthetic pharmaceutical agents. In the present study, a series of seven distinctively modified 2-pyridone derivatives were investigated with the aim of elucidating their potential in mitigating neuroinflammatory responses and conferring neuroprotection. To evaluate the properties of these derivatives, lipopolysaccharide (LPS)-stimulated BV2 microglial cells were used as experimental model. The metabolic activity of the cells and the production of inflammatory mediators, including reactive oxygen species (ROS), nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) were determined. The neuroprotective effect of investigated 2-pyridone derivatives was explored using a BV2 supernatant transfer model on SH-SY5Y neuronal cells. Molecular docking studies were conducted on proteins of interest associated with the LPS-induced BV2 inflammatory pathway, with the aim of unraveling potential underlying mechanisms responsible for the observed activities. Our findings demonstrated significant anti-neuroinflammatory properties exhibited by the investigated 2-pyridone derivatives, as evidenced by their ability to suppress the production of ROS, NO, IL-6, and TNF-α by LPS-stimulated BV2 cells. Moreover, a neuroprotective effect was observed in the microglial supernatant transfer model involving SH-SY5Y neuronal cells. The molecular docking studies suggested that investigated 2-pyridone derivatives might exert their anti-neuroinflammatory actions through interactions with proteins associated with the TLR4 pathway and inducible nitric oxide synthase. In conclusion, this study indicates that investigated 2-pyridone derivatives possess the potential to alleviate neuroinflammation mediated by microglia and protect neighboring neurons from damage, qualifying them for further investigation in neurodegenerative diseases associated with neuroinflammation.

Keywords: 2-pyridones; microglia; anti-neuroinflammatory potential; neuroprotective potential; molecular docking