Design, synthesis and biological evaluation of novel quinazoline-based anti-inflammatory agents acting as PDE4B inhibitors

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Abstract

A novel series of quinazoline based compounds (IIIa–d, VIa–f, IXa–f) were designed, synthesized and screened for their inhibitory activity towards the PDE4B isoform. The in vivo anti-inflammatory effect of the titled compounds (IIIa–d, VIa–f, IXa–f) as well as their effect on the level of tumor necrosis factor (TNF-α) were evaluated. Among all of the synthesized compounds, IXb, IXd and IXf, exhibited good inhibitory activity against PDE4B enzyme with inhibition percentages of 42, 62 and 68%, respectively. Most of the tested compounds showed potent anti-inflammatory activity compared to indomethacin with a marked decrease in TNF-α level. The ulcerogenic effect of the tested compounds was also examined. The gastric mucosa of the tested animals remained intact after oral administration of the hit compounds. Additionally, docking study was used to explore the possible binding mode of the active compounds on the PDE4B enzyme as well as to illustrate the selectivity of the active hits on the PDE4B isoform.

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