Synthesis and Computational Analysis of a New 5-(4-pyridil)-4,5-dihydroisoxazoles Derivates with Modulation of TNF-a Release

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The excessive production of the pro-inflammatory cytokines TNF-a, high mobility group Box 1 (HMGB1) and other inflammatory molecules by immune cells and their subsequent release into the circulation are associated with unrestrained inflammation. In a recent study, preliminary data showed the capacity of VGX-1027 [[(S,R)-3-phenyl-4,5-dihydro-5-isoxasole acetic acid] to inhibit the increase of circulating levels of TNF-a in LPS challenged mice. The 4,5-dihydroisoxasole is a five membered nitrogen/oxygen-containing heterocycle formed in relatively high yields through a [3+2]-cycloaddition reaction. In this work, we evaluated the modulation of TNF-a release by some different new 4,5-dihydroisoxasole synthesized by [3+2]-cycloaddition reaction using 4-vinylpyridine as a dipolarophile and four different aldheydes as a nitrile oxide precursor. These derivatives were prepared in low yields (16–50%) and their structures were elucidated by IR, ^{1}H, ^{13}C NMR and MS. The biological results showed that the 4,5-dihydroisoxazoles derivates reduced the secretion of TNF-a from murine macrophages stimulated *in vitro* with lipopolysaccharide (LPS), being compound 3-(3-chloro-phenyl)-5-(4-pyridil)-4,5-dihydroisoxazole the most active. Computational analysis of frontier orbital HOMO-LUMO, molecular electrostatics potential map (MEP) and dipole moment were performed to gain insight into the SAR aspects. This study pointed the m-chloro substituted derivative [3-(3-chloro-phenyl)-5-(4-pyridil)-4,5-dihydroisoxazole] as a leading compound for the development of new analogs.

Keywords: pro-inflammatory cytokines, TNF-a, 4,5-dihydroisoxasole, cycloaddition reaction.