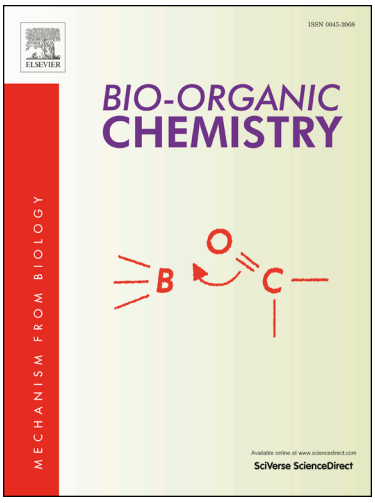

1,2,3-triazole tethered Indole-3-glyoxamide derivatives as multiple inhibitors of 5-LOX, COX-2 & Tubulin: Their anti-proliferative & anti-inflammatory activity

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1,2,3-triazole tethered Indole-3-glyoxamide derivatives as multiple inhibitors of 5-LOX, COX-2 & Tubulin: Their anti-proliferative & anti-inflammatory activity

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Abstract:

To evaluate the role of COX-2 and 5-LOX as dual inhibitors in controlling the cancer cell proliferation, a set of two series having 42 compounds of 1, 2, 3-Tethered Indole-3-glyoxamide derivatives were synthesized by employing click chemistry approach and were also evaluated for their *in vitro* cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX) inhibitory activities with *in vivo* anti-inflammatory and *in vitro* anti-proliferative potencies. Among the compounds tested, compounds **11q** and **13s** displayed excellent inhibition of COX-2 (IC_{50} 0.12 µM) with good COX-2 selectivity index (COX-2/COX-1) of 0.058 and 0.046 respectively. Compounds **11q** and **13s** also demonstrated comparable 5-LOX inhibitory activity with IC_{50} 7.73 and 7.43 µM respectively to that of standard Norhihydroguaiaretic acid (NDGA: IC_{50} 7.31 µM). Among all the selected cell lines, prostate cancer cell line DU145 was found to be susceptible to this class of compounds. Among all the tested compounds, compounds **11g**, **11i, 11k, 11q, 13r, 13s** and **13u** demonstrated excellent to moderate anti-proliferative activity with IC_{50s} ranging between 6.29-18.53 µM. Compounds **11q** and **11g** demonstrated better anti-proliferative activities against DU145 cancer cell line with IC_{50} values 8.17 and 8.69 µM respectively when compared to the standard drug etoposide (VP16; IC_{50} 9.80 µM). Compounds **11g, 11k, 11q, 13s** and **13u** showed good dual COX-2/5-LOX inhibitory potentials with excellent anti-proliferative activity. Results from carrageenan-induced hind paw edema demonstrated that compounds **11b**, **11l**, **11q** and **13q** exhibited significant anti-inflammatory activity with 69-77% inhibition at 3h, 75-82% inhibition at 5h when compared to the standard drug indomethacin (66.6% at 3h and 77.94% at 5h). Ulcerogenic study revealed that compounds **11q** and **13q** did not cause any gastric ulceration. *In vitro* tubulin assay resuted that compound **11q** interfered with microtubulin dynamic and act as tubulin polymerization inhibitor. *In silico* molecular docking studies demonstrated that compounds **11q** and **13s** are occupying the colchicines binding site of tubulin polymer and **11q** illustrated very good binding affinities towards COX-2 and 5-LOX.

Keywords: Indole-3-glyoxamide derivatives, 1,2,3-triazoles, COX-1; COX-2; 5-LOX; Tubulin; Anti-proliferation.