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Synthesis, anti-inflammatory screening, molecular docking, and COX-1,2/-5-LOX inhibition profile of some novel quinoline derivatives

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Abstract:

New quinoline compounds comprising pyrazole scaffold through different amide linkages were synthesized. The synthesized compounds were evaluated for their anti-inflammatory activity. Eight compounds (5c, 11b,c, 12c, 14a,b, 20a and 21a) were found to exhibit promising anti-inflammatory profiles in acute and sub-acute inflammatory models. They were screened for their ulcerogenic activity and none of them showed significant ulcerogenic activity comparable to the reference drug celecoxib and are well tolerated by experimental animals with high safety margin (ALD_{50} > 0.3 g/kg). Compounds 5c, 11b,c, 12c, 14a,b, 20a and 21a showed significant in vitro LOX inhibitory activity higher than that of zileuton. In vitro COX-1/COX-2 inhibition study revealed that compounds 12c, 14a,b and 20a showed higher selectivity towards COX-2 than COX-1. Among the tested compounds, 12c, 14a and 14b showed the highest inhibitory activity against COX-2 with an IC_{50} values of 0.1, 0.11 and 0.11 μM respectively. The docking experiments attempted to postulate the binding mode for the most active compounds in the binding site of COX-2 enzymes and confirmed the high selectivity binding towards COX-2 enzyme over COX-1.

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