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Design and synthesis of new amide base derivatives of 3-phenyl glutaric acid as soluble epoxide hydrolase inhibitors

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Abstract: Human soluble epoxide hydrolase (sEH) enzyme converts Epoxyeicosatrienoic acids (EETs) to their corresponding hydrated products by catalyzing the addition of water to the epoxide moiety. By inhibition of sEH enzyme, the amount of EETs increases. EETs relax vascular conduit and dilate renal afferent arterioles and increase sodium renal excretion. In addition, EETs modulate leukocyte adhesion, platelet aggregation, vascular smooth muscle cell migration and thrombolysis in preclinical animals. Therefore, Inhibitors of sEH represent a novel pharmaceutical approaches for treating cardiovascular related diseases. The most potent sEH inhibitors reported in literature have poor pharmacokinetic profile. Therefore, new scaffolds are needed for the therapeutic applications.

Ethylacetoacetate was reacted with benzaldehyde in the presence of piperidine to give corresponding diester which was treated with aqueous NaOH 50% followed by reaction with acetic anhydride to obtain the corresponding anhydride. Finally new amide derivatives was synthesized from the reaction of the aromatic and aliphatic amines with 4-phenyldihydro-2H-pyran-2,6(3H)-dione in dry dioxane.

In this research, new amide base derivatives of 3-phenyl glutaric acid were designed. These novel compounds were synthesized in acceptable yield and their structure were approved using instrumental methods including IR, Mass and ^{1}HNMR spectroscopy. Docking study on the designed sEH inhibitor confirms that the amide groups of the analogues fit in the hydrolase catalytic pocket of X-ray crystal structure of sEH and have a suitable distance from the three amino acids of Tyr383, Tyr466 and Asp335 for effective hydrogen bonding.

In conclusion, new amide-based compounds as sEH inhibitors were investigated. The docking study shows favorable results and the designed structures were synthesized and characterized by IR, Mass and ^{1}HNMR spectra.

Keyword:
Synthesis ; 3-phenyl glutaricacid; soluble epoxidehydrolase inhibitors