Design and synthesis of the novel amide derivatives of isoindoline-1,3-dione as soluble epoxide hydrolase inhibitors

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Abstract: Soluble epoxide hydrolase (sEH) is an enzyme that converts epoxyeicosatrienoic acids (EETs) to dihydroxyeicosatrienoic acids (DHETs) which show lower activity and better water solubility in comparison to EETs. By inhibition of the sEH enzyme, the amount of cellular EETs which have different physiological activities such as vasodilatory action and regulation of adhesion molecules, platelet aggregation, cellular migration and thrombolytic nature increase. Inhibitors of the sHE enzyme represent new approach to treat hypertension, atherosclerosis and inflammation. Since most of the reported inhibitors have inappropriate pharmacokinetic profile, these compounds are not suitable for clinical uses. In order to develop sEH inhibitors with improved physicochemical properties while maintaining potency, some amide based structures were designed, synthesized and structurally confirmed. Potassium phthalimid was reacted with para-nitrobenzoyl bromide through nucleophilic substitution to afford 2-(4-nitrobenzyl)isoindoline-1,3-dione. The final products were synthesized through the reduction of the nitro group followed by treatment with para substitute benzoyl chloride derivatives. In this study, some new amide derivatives against sEH were designed. These compounds were synthesized in good yield and elucidated by IR, NMR and Mass spectra. The docking studies showed that the designed structures fit properly in the active site of the enzyme and have a suitable distance from aspartate and tyrosine residues for effective hydrogen bonding. In Conclusion, the novel amide base compounds as novel soluble epoxide hydrolase inhibitors were designed and synthesized. Docking studies revealed that these structures could have efficient inhibitory effects against soluble epoxide hydrolase.

Keyword: soluble epoxide hydrolase; inhibitor; synthesis