Design and synthesis of novel 1,2,4-triazole derivatives as soluble epoxide hydrolases inhibitors

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Abstract

Introduction: Soluble epoxide hydrolase (sEH) inhibitors have been shown to effectively increase the levels of epoxyeicosatrienoic acids and reduce the levels of dihydroxyeicosatrienoic acids, which may be translated to therapeutic potentials for hypertension, diabetes, stroke, dyslipidemia, pain, immunological disorders, eye diseases, neurological diseases and other indications. Since most sEH inhibitors have poor pharmacokinetic properties, development of novel inhibitors is a great deal of attention.

Methods and Results: Based on the structure activity relationship of soluble epoxide hydrolase inhibitors and docking studies, some novel compounds with amide moiety and triazole ring as a first and second pharmacophore respectively were designed. These structures were synthesized through 4 step reaction with proper yields. Initially, 4-nitrobenzoyl chloride was reacted with hydrazine hydrate and then in the presence of benzonitrile and catalytic amounts of copper iodide, 1,2,4-triazole was closed. Final products were obtained by reduction of nitro group and reaction with various benzoyl chlorides. Docking studies on the designed sEH inhibitors confirm that the amide groups of the analogues fit properly in the active site of sEH and have a suitable distance from the amino acids of Tyr466 and Asp335 for effective hydrogen bonding. These novel compounds were synthesized in appropriate yield and their structure was approved by instrumental methods including IR, Mass, HNMR and ^{C}NMR spectroscopies.

Conclusions: In conclusion, some novel amide-based soluble epoxide hydrolase enzyme inhibitors with a 1,2,4-tri azole as a novel secondary pharmacophore were designed, synthesized and structurally approved by IR, NMR and Mass spectra.

Key words: Inhibitor, soluble epoxide hydrolase, triazole.