

Design and synthesis of novel (E)-2-(4-fluorophenyl)-2-(hydroxyimino)-1-(2-(methylthio)pyrimidin-4-yl)ethanone as potential protein kinase inhibitors and identifying cytotoxic effect

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Background and Aims: Inhibition of the biosynthesis of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 via p38 has been an approach toward the development of a disease modifying agent for the treatment of chronic inflammation and autoimmune disease. We have identified a novel series of potent p38 MAP kinase inhibitors through structure-based design which due to their extend molecular architecture bind, in addition to the ATP site, to allosteric pocket.

Methods: The development of a new core structure of p38 inhibitors (E)-2-(4-fluorophenyl)-2-(hydroxyimino)-1-(2-(methylthio)pyrimidin-4-yl)ethanone is described. Raw material in this project was 2-mercapto-4-methylpyrimidine hydrochloride. To a solution of 2-mercapto-4-methylpyrimidine hydrochloride in ethanol and 1.0M sodium hydroxide (2 equiv) was added methyl iodide (1 equiv). the reaction was stirred for 16 h, evaporated to half volume, and extracted with ethyl acetate. the combined organic phases were washed with water and brine, dried (sodium sulfate), and then concentrated to yield 90% as an oil. 4-((Z)-2-(4-fluorophenyl)prop-1-enyl)-2-(methylthio)pyrimidine was obtained after the different stages. And at the end, final compound was (E)-2-(4-fluorophenyl)-1-(2-(methylthio)pyrimidin-4-yl)-2-propoxyiminoethanone. The best experimental conditions were chosen for each stage with different experiences and optimal efficiency of reaction was high. Their chemical structure identified by HNMR and IR spectroscopy.

Results: We have identified a novel series of potent p38 MAP kinase inhibitors through structure-based design which due to their extend molecular architecture bind, in addition to the ATP site, to allosteric pocket.

Conclusions: Therefore derivations of di-azin synthesis with S-CH₃ substituates and their effect is under review.

Keywords: p38 inhibitors; MAP kinase; Antiinflammatory; Cytokines