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In Silico and In Vivo Evaluation of Pyridinyltriazoles as Inhibitors of p38 MAP Kinase

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Objective(s)
Inhibitors of p38 MAP kinase are considered as suitable target in the treatment of inflammatory diseases such as rheumatoid arthritis and bowel inflammatory diseases. The development of 5-alkylthio-1-aryl-2-(4-pyridinyl) triazoles as inhibitors of p38 MAP kinase is described. These are analogues of 4- pyridinyl imidazole p38 MAP kinase inhibitor reported by Merck Research Laboratories, in which imidazole ring has been replaced with triazole.

Materials and Methods
Reaction of pyridine-4-carboxylic acid hydrazide 1 and arylisothiocyanate (2a, b) gave the intermediate thiourea derivative 3a, b (Figure 2). Refluxing of the latter in aqueous saturated sodium carbonate gave 1-aryl-5-mercapto-2-(4-pyridinyl) triazoles 4a, b. Treatment of 4a, b with alkyl iodide afforded the desired 5-alkylthio-1-aryl-2-(4-pyridinyl) triazoles (5a-d). P38 MAP kinase inhibitory activity of the synthesized compounds was evaluated *in vitro* by ELISA method and also by molecular docking.

Results
Compound 5c at 1 µM concentration and compound 5d at 1 µM and 10 µM significantly inhibited the p38 phosphorylation. These inhibitory effects are equal to those of standard compound SB202190 and no significant differences were observed.

Conclusion
We demonstrated that both tested compounds have inhibitory effect on p38 MAP kinase and we did not find significant difference between their inhibitory effects and those of standard inhibitor SB202190.

Keywords: Inhibitors, p38 MAP kinase, Pyridinyl, imidazole