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Design and development of ureas and amides as p38 kinase inhibitors

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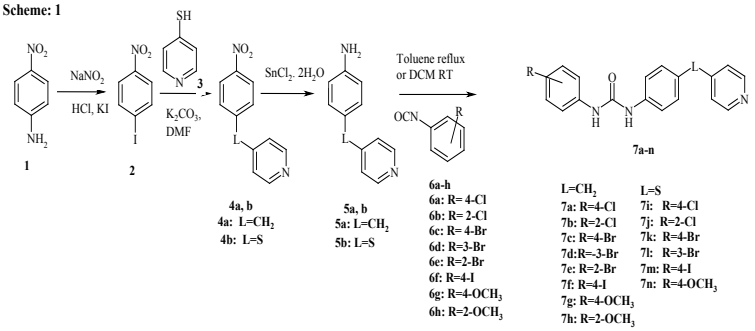
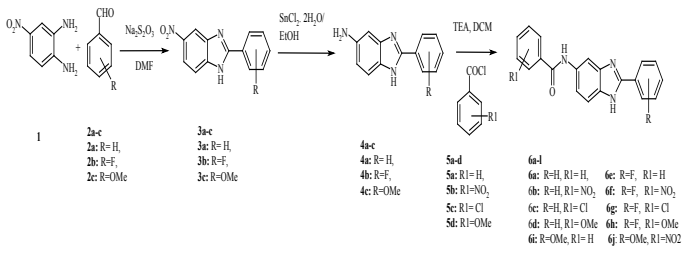
Inflammation is a complex pathological condition associated with exaggerated human immune system involving various activated immune cells and bio-molecules. Current therapeutic approaches to the treatment of inflammatory diseases are centered on inhibition of cyclooxygenases and are associated with undesirable gastrointestinal and cardiovascular side effects. The p38 protein kinase is a serine-threonine mitogen activated protein kinase, which plays an important role in inflammation and arthritis. Inhibition of p38 kinase is highly desired in inflammatory diseases and low molecular weight p38 kinase inhibitors show same therapeutic benefits like biological anti-cytokines but offer advantages in terms of oral dosage and affordable cost. A series of diaryl urea compounds have been synthesized based on the 3D QSAR model and structure based docking studies. The intermediates amines were treated with substituted aromatic isocyanates which afforded the diaryl urea compounds (Scheme 1). All the purified compounds were characterized and subjected for p38 kinase inhibitory and anti-inflammatory activities. Compound 7f demonstrated IC50 value of 1.09 µM in p38 kinase assay and 79.41% inhibition of rat paw edema at the 2nd hour of carrageenan challenge. The molecular docking studies of synthesized compounds indicated some of the important hydrogen bonding interactions and also revealed the minor change in the binding pose when compared to BIRB796. A series of benzimidazoles were designed from our in house urea derivatives and designed molecules have been synthesized from 4-nitro-1, 2-diaminobenzene (Scheme 2). The final compounds were screened for *in vitro* p38 kinase inhibitory and *in vivo* anti-inflammatory activity. Three compounds from the series demonstrated nearly 50% inhibition of p38 kinase in the *in vitro* screening method at 10 µM concentration and two molecules exhibited greater than 75% inhibition of paw oedema volume during the first hour. The docking study of synthesized molecules revealed a new binding pose in ATP binding pocket.

Scheme: 1



Scheme: 2



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