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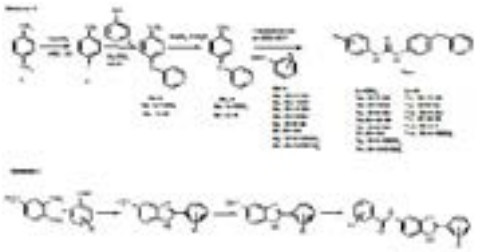
Design and development p38 kinase inhibitors

Mitogen activated protein kinases (MAP kinase) play crucial roles in the signal transduction pathways and are activated by various extracellular signals triggered by growth factors, physicochemical stress and cytokines. p38 Kinase plays a vital role in inflammation mediated by tumor necrosis factor-a (TNFα) and interleukin-1β (IL-1β) pathways and inhibitors of p38 kinase provide effective approach for the treatment of inflammatory diseases. Pyridinyl and pyrimidinyl imidazoles, selectively inhibit p38a MAP kinase, are useful in the treatment of inflammatory diseases like rheumatoid 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. Current therapeutic approaches to the treatment of inflammatory diseases are centered on cycloxygenase enzymes but are associated with undesirable gastrointestinal and cardiovascular side effects. A drastic shift in the attention of medicinal chemists is perceived towards p38 kinase as an important molecular target in recent years. 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. All the purified compounds were characterized and subjected for p38 kinase inhibitory and anti-inflammatory activities. Compound 7f demonstrated IC_{50} 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. 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.



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