Tetrasubstituted Imidazole Inhibitors of cytokine release
Optimizing the N-1 position for p38 MAP kinase inhibition and low CYP-450 interaction

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Pyridinylimidazoles are known as potent inhibitors of p38 MAP Kinase. The structures known so far have the disadvantage of inhibiting CYP450 enzymes. Responsible for this interaction are two structural properties of these compounds: the pyridinyl- and the imidazole –ring. Aim of this work was to modify SB-type structures to optimize p38 inhibition while lowering CYP450-interference at the same time. Our strategy was to substitute the pyridinyl-ring by aminoalkyl- and aminoacyl-substituents (R1) and to introduce alcohols, ethers, amines, acetales and sulfides at the N1 position (R2).

Most potent compounds showed 20-fold increase in potency and strongly reduced CYP-450 inhibition (1A2, 2D6).