ML 3403 - Pharmacological characterization of a potent p38-MAP kinase inhibitor

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ML 3403 ({4-[5-(4-Fluoro-phenyl)-2-methylsulfanyl-1H-imidazol-4-yl]-pyridin-2-yl}-(1-phenyl-ethyl)-amine) was selected as a promising p38-inhibitor. Its pharmacological properties were investigated and compared to those of SB203580. The p38-mediated phosphorylation of immobilized ATF-2 was inhibited with an IC_{50} of 380 nM (SB203580: IC_{50}=760 nM). At a concentration of 10 μM, a relevant inhibition was observed for the protein kinases JNK2α2 (80%) and JNK3 (98%), and for the cytochrome P450 isoenzymes 3A4, 1A2, 2C9 and 2C19. In human mononuclear cells (MCs) and whole blood (WB), the LPS-induced synthesis of TNFα and IL-1β was inhibited with IC_{50}-values of 200 nM/2700 nM (TNFα) and 30 nM/1000 nM (IL-1β). The addition of serum albumin to MC culture medium had a slight influence on the potency. Following oral administration of ML 3403 to male BALB/c mice, the GalN/LPS-induced production of TNFα was suppressed dose-dependently with an ED_{50} of 1.33 mg/kg (SB203580: ED_{50} 2.7 mg/kg). The pharmacological profile of ML 3403 has been considered promising, and deserves further exploration of this structural motif.