MAP kinases are involved in numerous signaling processes that are crucial for normal function of cells and organisms. MAP kinases are mainly activated via the canonical three-tiered cascade leading to dual phosphorylation on adjacent Thr-180 and Tyr-182 (p38α numbering) located on the phosphorylation lip. For p38α several alternative activation pathways and modes have been identified where one is induced by T-cell receptor activation and subsequent phosphorylation of p38α on the distinctive Tyr-323 distal from the phosphorylation lip by ZAP-70 tyrosine kinase. Consequent to Tyr-323 phosphorylation, autoactivation occurs in trans, resulting in monophosphorylation of Thr-180. This alternative pathway differs in its substrate selectivity profile from the canonical one. The structures of intrinsically active 323-site mutants considered to emulate the phosphorylated form, exhibit conformational changes depicting the molecular basis for autophosphorylation and subsequent activation. An additional activation mode was revealed while screening for Akt phosphatidylinositol analogues (PIAs) inhibitors. It was also shown that these lipid molecules bind and activate p38α inducing autoactivation and apoptosis. Perifosine, an Akt inhibitor, also exhibit p38α activation properties similarly to those of PIAs. The crystal structures of p38α in complex with activating lipid molecules identify a new activation site in the p38α C-lobe. In addition conformational changes in the αEF/αF loop could paly an essential role in the autoactivation properties. This site could become a platform towards the design of specific inhibitors and activators of p38α.