BIOLOGICAL ACTIVITY

Description
PRT062607 (P505-15; PRT-2607; BIIB-057) is a highly specific and potent inhibitor of Syk with IC50 of 1-2 nM; >80-fold selective for Syk than Fgr, Lyn, FAK, Pyk2 and Zap70. IC50 value: 1-2 nM [1]. Target: Syk kinase inhibitor in vitro: In human whole blood, P505-15 potently inhibited B cell antigen receptor-mediated B cell signaling and activation (IC50 0.27 and 0.28 μM, respectively) and Fce receptor 1-mediated basophil degranulation (IC50 0.15 μM) [1]. P505-15 successfully inhibited SYK-mediated B-cell receptor signaling and decreased cell viability in NHL and CLL [2]. PRT318 and P505-15 effectively antagonize CLL cell survival after BCR triggering and in nurse-like cell-co-cultures. Moreover, they inhibit BCR-dependent secretion of the chemokines CCL3 and CCL4 by CLL cells, and leukemia cell migration toward the tissue homing chemokines CXCL12, CXCL13, and beneath stromal cells. PRT318 and P505-15 furthermore inhibit Syk and extracellular signal-regulated kinase phosphorylation after BCR triggering [3]. In vivo: Similar levels of ex vivo inhibition were measured after dosing in mice (Syk signaling IC50 0.32 μM). Oral administration of P505-15 produced dose-dependent anti-inflammatory activity in two rodent models of rheumatoid arthritis [1]. Oral dosing in mice prevented BCR-mediated splenomegaly and significantly inhibited NHL tumor growth in a xenograft model. In addition, combination treatment of primary CLL cells with P505-15 plus fludarabine produced synergistic enhancement of activity at nanomolar concentrations [2].

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