

4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK-INHIBITORS

Field of the invention

The present invention relates to 6-5 membered fused pyridine ring compounds, to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of 6-5 membered fused pyridine ring compounds in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

Background of the invention

B lymphocyte activation is key in the generation of adaptive immune responses. Derailed B lymphocyte activation is a hallmark of many autoimmune diseases and modulation of this immune response is therefore of therapeutic interest. Recently the success of B cell therapies in autoimmune diseases has been established. Treatment of rheumatoid arthritis (RA) patients with Rituximab (anti-CD20 therapy) is an accepted clinical therapy by now. More recent clinical trial studies show that treatment with Rituximab also ameliorates disease symptoms in relapsing remitting multiple sclerosis (RRMS) and systemic lupus erythematosus (SLE) patients. This success supports the potential for future therapies in autoimmune diseases targeting B cell immunity.

Bruton tyrosine kinase (Btk) is a Tec family non-receptor protein kinase, expressed in B cells and myeloid cells. The function of Btk in signaling pathways activated by the engagement of the B cell receptor (BCR) and FcεR1 on mast cells is well established. In addition, a function for Btk as a downstream target in Toll like receptor signaling was suggested. Functional mutations in Btk in human results in the primary immunodeficiency disease called XLA which is characterized by a defect in B cell development with a block between pro- and pre-B cell stage. This results in an almost complete absence of B lymphocytes in human causing a pronounced reduction of serum immunoglobulin of all classes. These finding support the key role for Btk in the regulation of the production of auto-antibodies in autoimmune diseases. In addition, regulation of Btk may affect BCR-induced production of pro-inflammatory cytokines and chemokines by B cells, indicating a broad potential for Btk in the treatment of autoimmune diseases.

With the regulatory role reported for Btk in FcεR-mediated mast cell activation, Btk inhibitors may also show potential in the treatment of allergic responses [Gilfillan et al, Immunological Reviews **288** (2009) pp149-169].

Furthermore, Btk is also reported to be implicated in RANKL-induced osteoclast differentiation [Shinohara et al, Cell **132** (2008) pp794-806] and therefore may also be of interest for the treatment of bone resorption disorders.