COMPOUNDS, COMPOSITIONS, AND METHODS FOR TREATING T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

FIELD

In an aspect, the disclosure provides for compounds, compositions, and methods of administering the compounds and compositions to a patient in need thereof. In another aspect, the disclosure relates to compounds and compositions for treating cancer, for example, lymphoid leukemia or lymphoma. The disclosure further provides for compounds which inhibit two phosphoinositide 3-kinase (PI3K) isoforms, γ and δ, pharmaceutical compositions comprising such compounds, and methods of using the compounds and/or pharmaceutical compositions for treatment, amelioration, and/or prevention of diseases arising from PI3K hyperactivity, such as non-Hodgkin's lymphoma.

BACKGROUND

The PI3K signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K signaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome. PI3K/Akt signaling pathway promotes the growth, proliferation and survival of many types of tumors.

PI3Ks exist as heterodimeric complexes, including a p110 catalytic (classified as α, β, γ, or δ) and a p50, p55, p85, or p101 regulatory subunit. PI3Ks can be divided into 2 subclasses, Ia and Ib, defined by mechanism of activation.

Class Ia PI3Ks include the p110α, p110β, and p110δ catalytic domains, each of which associates with a regulatory protein and is activated directly or indirectly on engagement of several cell surface receptors, including TCR.

Class Ib PI3Ks consist only of p110γ, which associates with the p101 adaptor molecule and is primarily stimulated by G protein-coupled receptors.

Initial activation of this pathway, through growth factor interactions with a cell surface receptor for instance, results in the phosphorylation of specific lipids contained within the inner layer of the plasma membrane, yielding the second messenger