TITLE OF THE INVENTION: IMIDAZOPYRIDAZINE COMPOUNDS ~~AND USES THEREOF~~ WITH ACTIVITY AS ALK2 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to, and the benefit of, Provisional Application No. 63/038,410, filed June 12, 2020 entitled "IMIDAZOPYRIDAZINE COMPOUNDS AND USES THEREOF", the entirety of which is incorporated herein by reference.

FIELD OF THE INVENTION

The disclosure provides imidazopyridazine compounds as well as their compositions and methods of use. The compounds modulate activin receptor-like kinase-2 (ALK2) activity and are useful in the treatment of various diseases including cancer.

BACKGROUND OF THE INVENTION

Bone morphogenetic protein (BMP) signaling belongs to the transforming growth factor beta (TGF-β) superfamily and TGF-β signaling ligands include more than 25 different ligands: TGF-β growth and differentiation factors, BMPs and Activins. The binding of BMP ligands leads to the assembly of tetrameric receptor complexes composed of two constitutively-active type II receptor serine/threonine kinases (BMPRII, ACTRIIA, or ACTRIIB) and activate two type I receptor serine/threonine kinases (ALK1, ALK2, ALK3, or ALK6). Furthermore, the activated type I receptors phosphorylate BMP receptor responsive SMAD proteins 1/5/8 and the activated SMAD1/5/8 associated with co-SMAD4 translocate to the nucleus to regulate gene transcription. (Ross, S.L., et al. Cell Metabolism 2012, 15, 905-917; Blobe, G.C., et al. New England Journal of Medicine 2000, 342, 1350-1358).

BMPR kinase activin A receptor, type I (ACVR1) is also called activin receptor-like kinase-2 (ALK2). It is composed of a ligand-binding extracellular domain and a cytoplasmic domain with serine/threonine specificity. ALK2 has been reported to mediate multiple human diseases (Massague, J., et al. Cell 2000, 103, 295-309; Taylor, K.R., et al. Cancer Research 2014, 74, 4565-4570). ALK2 and ALK3 have been shown to play an essential role in regulating the hepcidin levels and affecting the anemia of chronic disease (Andriopoulos, B., et al. Nature Genetics 2009 41, 482-487; Steinbicker, A.U., et al. Blood 2011, 118, 4224-4230; Steinbicker, A.U., et al. Blood 2011, 117, 4915-4923). Hepcidin is a small peptide hormone primarily synthesized in hepatocytes and reduces both duodenal iron absorption and