Discovery of conformationally constrained ALK2 inhibitors for the treatment of Diffuse Intrinsic Pontine Glioma (DIPG)

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Abstract

Despite considerable research on new therapeutics to treat DIPG, a universally fatal grade IV pediatric CNS tumor located in the pons region of the brainstem, there has been minimal progress. Somatic missense mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1 gene encoding activin receptor-like kinase-2 (ALK2) are present in approximately 33% of children with DIPG, prompting our initial efforts towards the development of **M4K2009**, a 3,5-diphenylpyridine ALK2 inhibitor. Looking to improve potency, selectivity, and brain penetration, we subsequently designed, synthesized, and evaluated a first-in-class set of 5- to 7-member ether-linked and 7-member amine-linked conformationally constrained ALK2 inhibitors including **M4K2308, M4K2281, M4K2304** and **M4K2306**. Overall, these new compounds are highly potent (ALK2 IC_{50} < 10 nM, nanoBRET ALK2 IC_{50} < 20 nM), selective (>100-fold over ALK5), brain-penetrant ($C_{brain,4h}/C_{plasma,4h}$ > 3, 10 mg/kg, NOD-SCID male mice) and show in vivo exposure ($C_{plasma,6h}$ = 1−2 μM, 25 mg/kg, NOD-SCID male mice). In particular, **M4K2308** displayed a good balance of potency and DMPK properties and is currently undergoing preclinical evaluation by M4K Pharma.