Structure-based design of MRTX1719: an MTA-cooperative PRMT5 Inhibitor for treatment of MTAP-deleted cancers

Robin Gunn[1]

[1]Mirati Therapeutics

gunnr@mirati.com

The methylthioadenosine phosphorylase (MTAP)-encoding gene is co-deleted with p16/CDKN2a in ~10% of human cancers, leading to elevated levels of MTAP substrate, methylthioadenosine (MTA) in these cancers. Protein arginine methyltransferase 5 (PRMT5) binds MTA making the resulting PRMT5•MTA complex, a synthetically lethal drug target for the treatment of MTAP-deleted cancers. Here, we report the discovery of a novel series of 4-(aminomethyl)phthalazin-1(2H)-one compounds identified via a fragment-based screen of the PRMT5•MTA complex by SPR. Fragment growth supported by structural insights from x-ray crystallography coupled with optimization of pharmacokinetic properties aided the discovery of MRTX1719. MRTX1719 is a clinical-stage, PRMT5•MTA selective inhibitor with potential as a precision medicine for treating MTAP-deleted tumors.