Abstract

The PI3K/Akt pathway is constitutively activated in a large proportion of human cancers. mTOR kinase plays a vital role in this pathway as the key component of two independent signaling complexes (mTORC1 and mTORC2). Inhibition of mTOR kinase could therefore serve as an effective means of abrogating PI3K-dependent signaling. In addition, the activity of TORC1 is often aberrantly activated in a PI3K-independent manner enabling tumor cells to survive and proliferate despite the many negative influences of the tumor microenvironment. Therefore, targeting the activity of TORC1 and TORC2 would abrogate both PI3K signaling and the cancer cells’ ability to survive in the harsh environment of the tumor.

We report here the development of a potent and selective small molecule inhibitor of mTOR kinase designated AR-mTOR-26. On enzyme this compound exhibits low single digit nM activity against isolated mTOR kinase with >40-fold selectivity against the α, β and δ isoforms of PI3K as well as a panel of over 250 ser/thr and tyrosine kinases. On cells AR-mTOR-26 potently inhibits TORC1/2-dependent readouts pAKT(S473), p4E-BP1(S37/46) and pS6(S235/6) yet is significantly inactive against the PI3K-dependent readout pAKT(T308) confirming its selectivity against Class I PI3K-kinases. This cellular potency readily translates into broad anti-proliferative activity against a wide array of solid tumor and hematological cancer cell lines irrespective of mutational status (i.e. KRAS, PTEN, PIK3CA, etc.). AR-mTOR-26 possesses exceptional pharmacokinetic properties across multiple species, including mouse with exposures predicted to be biologically active. The potential for in vivo activity was confirmed in two tumor xenograft models both in terms of tumor growth inhibition as well as inhibition of mTOR-relevant targets in the tumors.