Compounds from our PI3K/PKB program were selected to evaluate their PI3K/PKB activity identifying in such a way hits with weak dual PI3K/PKB activities. These hits came from an internally generated collection of macrocycles, which were explored by using dual PI3K/PKB activities. Crystal structure of the hits in PPII protein helped us to understand the key interactions of these compounds required for PPII activity. Taking this into account, a chemical exploration was done around them trying to balance the dual (PI3K, PI3K/mTOR) or triple (PI3K, PIM, mTOR) activities and optimize the drug-like properties of the compounds. As a result of these exploration compounds ETP-539/BL-202 and ETP-339/BL-301 were identified.

Identification of PI3K/PKB and PIM/PI3K/PKB inhibitors

Biochemical and ADME profile of ETP-539/BL-202 and ETP-339/BL-301

Downregulation of PIM and PI3K/mTOR by dual and triple action inhibitors

Antiproliferative activity of dual and triple action inhibitors

Pharmacokinetic profile of ETP-539/BL-202 and ETP-339/BL-301 in mouse and rat exposure

Biochemical and ADME profile of ETP-539/BL-202 and ETP-339/BL-301

Downregulation of PIM and PI3K/mTOR by dual and triple action inhibitors

Antiproliferative activity of dual and triple action inhibitors

Pharmacokinetic profile of ETP-539/BL-202 and ETP-339/BL-301 in mouse and rat exposure

Compounds with dual PIM/PI3K or PIM/PI3K/mTOR inhibition activities have been developed. ETP-339/BL-202 (PI3K/PKB) and ETP-339/BL-301 (PI3K/mTOR) have been identified as selective orally bioavailable compounds.

Both ETP-339/BL-202 (PI3K/PKB) and ETP-339/BL-301 (PI3K/mTOR) showed more potent antiproliferative activity than PIM and PI3K selective inhibitors alone. This correlated with higher induction of apoptosis and strong downregulation of PIM, PI3K, mTOR pathways.

- Dual and triple compounds show synergistic effect in cancer cells lines over single agent compounds.
- ETP-339/BL-301 (PIM/mTOR) and ETP-339/BL-301 (PI3K/mTOR) showed antiproliferative activity in vitro, showing downregulation of PIM, PI3K, mTOR pathway biomarkers in PK/PD mechanistic studies, together with efficacy in GEMM of NSCLC at a low dose of 5mg/kg.

Conclusions