Wen Yun Hsueh et al., Chem Sci J 2017, 8:4 (Suppl)
DOI: 10.4172/2150-3494-C1-015

Discovery of Hec1/Nek2 inhibitor TAI-95 tosylate as first-in-class clinical candidate: Optimization of potency, oral pharmacokinetics and salt

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This poster presents the discovery of orally active TAI-95 tosylate, the Nek2/Hec1 inhibitor in clinical trial for cancer therapy. Designed and optimized from lead compound 4-aryl-N-phenylcarbonyl-2-aminothiazole, TAI-95 tosylate shows ~100-fold improved *in vitro* potency (IC_{50}: 14.8-21.1 nM), high oral AUC (66.6 μM•h) and good oral bioavailability (77.4%). Oral administration of TAI-95 shows significant *in vivo* activity on mice bearing human liver cancer Huh-7 and breast cancer BT474, MDA-MB-231 and MCF7 xenografts. It disrupts the interaction of Hec1 and Nek2 and leads to degradation of Nek2, chromosomal misalignment and apoptotic cell death, which are the cellular events of Hec1/Nek2 inhibition. TAI-95 showed synergistic activity in selected cancer cells with Doxorubicin, Paclitaxel and Topotecan and is inactive for non-cancerous cancer cells, a panel of kinases and hERG with IC_{50} values greater than 10 μM. Currently, it was in phase-I clinical trial to study its maximum tolerated dose, pharmacokinetics and responses on patients with advanced refractory solid tumors.

Biography

Wen Yun Hsueh has completed her Master's degree from the Department of Applied Chemistry at National Chiayi University, Taiwan. Currently she is pursuing PhD research at the same institute. Her research interests include chemistry and synthesis of heterocycles as anti-cancer agents.

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