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HS206, a selective inhibitor of Transforming growth factor β-activated kinase 1 (TAK1, MAP3K7)

Value Proposition

Transforming growth factor b-activated kinase 1 (TAK1) plays a key role in the signaling pathways of inflammation and cell survival. TAK1 is activated by a number of pro-inflammatory signals (e.g., TNFα), resulting in the induction of key inflammatory and pro-survival genes. TAK1 inhibition induces death of cancer cells and thus, TAK1 has emerged as a potential therapeutic target for cancer and inflammatory diseases. Despite the increasing interest in TAK1 as a potential therapeutic target, academia and industry alike have failed to develop selective small molecule inhibitors targeting TAK1. Previously identified inhibitors of TAK1 have not been advanced clinically, largely due to selectivity issues *in vivo*.

Technology

The inventors developed novel synthetic TAK1 inhibitors that show exquisite selectivity against all other protein kinases for TAK1. Of these molecules is HS-206: a previously unreported TAK1 inhibitor that blocks TNFa dependent signaling. HS-206 shows high selectivity against TAK1 over all other known kinases expressed in the human genome (left). The inventors also have *in vitro* data demonstrating the inhibitory potency of HS-206 against TAK1, as well as its ability to be well tolerated in mice in studies of maximum tolerated dose. Finally, in cell-based assays, HS-206 potently inhibits cell proliferation of certain tumor lines, including triple negative breast cancer cells.

Advantages

- Inhibitors work by blocking TNFa signaling without impacting other cellular functions
- Technology highly selective for TNFa signaling and could therefore out compete frontline anti-TNFa therapies on many levels, such as reducing cost and adverse side effects
- Small drug-like molecules that can be formulated for oral bioavailability

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