

## 28AB-ISMS15 **Discovery of Novel 2',4'-dimethyl-[4,5'-bithiazol]-2-yl Amino Derivatives as Orally-Bioavailable TRPV4 Antagonist for the Treatment of Pain**

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TRPV4 is one of a cation channel of the Transient Receptor Potential Vanilloid superfamily, which is activated by several stimuli such as hypo-osmotic, heat and chemical agonist 4-phorbol 12,13-didecanoate (4αPDD). TRPV4 is widely expressed in various tissues, and the activation of TRPV4 can induce many physiological responses, and involve the development of various diseases. Recently, it was revealed that selective and competitive TRPV4 antagonist for 4αPDD or osmotic stress showed an important role in pain. In our compound library, we identified 2',4'-dimethyl-[4,5'-bithiazol]-2-yl amino derivative as a novel TRPV4 antagonist by high-throughput screening against hypo-osmotic and 4αPDD stimuli. Some orally-bioavailable compounds possess analgesic activity in pain model was identified by hit to lead optimization study.