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Structure–Activity Relationship Studies and Synthesis of a Potent Transient Receptor Potential Vanilloid (TRPV1) Antagonist 4-[3-Chloro-5-[(1S)-1,2-dihydroxyethyl]-2-pyridyl]-N-[5-(trifluoromethyl)-2-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxamide (V116517) as a Clinical Candidate for Pain Management

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Capsaicin, the active ingredient of chili peppers, has been known for decades to specifically activate mammalian nociceptors and cause pain. Identification of TRPV1 antagonists has been the focus of drug discovery efforts over the past several years by a number of pharmaceutical companies. A series of novel tetrahydropyridinecarboxamide TRPV1 antagonists analogs were prepared and evaluated in an effort to optimize properties of previously described lead compounds from piperazinecarboxamide series in a close collaboration between Shionogi and Purdue. The compounds were evaluated for their ability to block capsaicin and acid-induced calcium influx in CHO cells expressing human TRPV1. The most potent of these TRPV1 antagonists were further characterized in pharmacokinetic, efficacy and body temperature studies. Based on its pharmacokinetic, in-vivo efficacy, safety, and toxicological properties, **V116517** was selected for further evaluation in human clinical trials.