[S7-4] [10/18/2002(Fri) 15:00-15:30/Hall A]

A Novel and Highly Potent Non-vanilloid VR Antagonist

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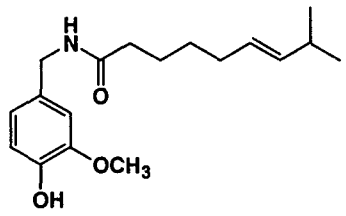
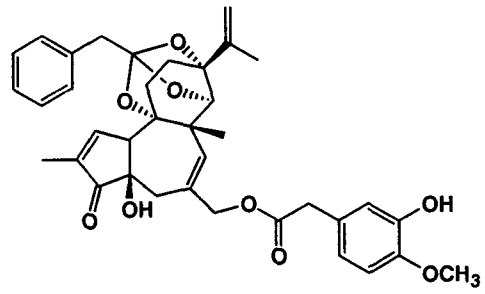
Since capsaicin was found as an excellent vanilloid receptor agonist, considerable efforts toward the development of a novel analgesic have been continued. However, the small therapeutic window between these effects and the excitatory side effects, such as hypothermia, bronchoconstriction, increased GI mobility, and hypertension, precluded the development of capsaicin as a systemic agent. In addition, the low oral bioavailability of capsaicin was a further problem for its therapeutic uses. Thus, recent studies on VR agonists or antagonists have focused on separating the excitatory effects of capsaicin analogs from the antinociceptive properties of these molecules. On the basis of the previous studies on vanilloid agonists and antagonists, as well as our recent exciting findings, we have looked for non-vanilloid VR antagonists by developing ideal vanilloid equivalents, which might provide the perfect analgesic effects without the side effects caused by vanilloid receptor agonists. We herein report a novel and highly potent non-vanilloid VR antagonists as a promising analgesic candidate.

During the course of our work on VR antagonist, we have identified a new class of potent and selective VR antagonists. These synthetic ligands act as potent inhibitor of Ca^{2+} uptake with IC_{50} value much better than capsazepine, and display a potent analgesic activity similar to that of indomethacin in vivo. Moreover, series of our novel VR antagonists are devoid of the important shortcomings of capsaicin, such as hypothermia and pungency. Furthermore, most importantly, they are very easy to synthesize and can be obtained in hundreds-gram quantities. At present, SC0030, one of the novel VR antagonists, is undergoing clinical trials with

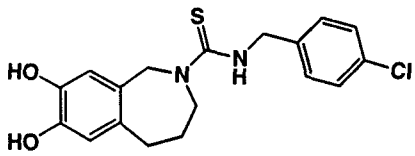
promising results. Ultimately, SC0030 could be useful not only as a tool to investigate the VR-mediated pain response but also as new lead for vanilloid drug development. In addition, intensive SAR studies will be reported.



Capsaicin



Resiniferatoxin



Capsazepine