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4-x display--inline-block" style="background: var(--highlight-yellow); color: inherit;">Picomolar, 4-x display--inline-block" style="background: var(--highlight-yellow); color: inherit;">selective, and subtype - specific small - molecule inhibition of TRPC1 / 4 / 5 channels

Rubaiy H.N.[a], Ludlow M.J.[a], Henrot M.[b], Gaunt H.J.[a], Miteva K.[a], Cheung S.Y.[a], Tanahashi Y.[a, c], Hamzah N.[d], Musialowski K.E.[a], Blythe N.M.[a], Appleby H.L.[a], Bailey M.A.[a] McKeown L.[a], Taylor R.[d], Foster R.[d], Waldmann H.[e], Nussbaumer P.[f], Christmann M.[b], Bon R.S.[a], Muraki K.[g], Beech D.J.[a]

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Abstract

The concentration of free cytosolic Ca^{2+} and the voltage across the plasma membrane are major determinants of cell function. Ca^{2+}-permeable non-4-x display--inline-block" style="background: var(--highlight-yellow); color: inherit;">selective cationic channels are known to regulate these parameters, but understanding of these channels remains inadequate. Here we focus on transient receptor potential canonical 4 and 5 proteins (TRPC4 and TRPC5), which assemble as homomers or heteromerize with TRPC1 to form Ca^{2+}-permeable non-4-x display--inline-block" style="background: var(--highlight-yellow); color: inherit;">selective cationic channels in many mammalian cell types. Multiple roles have been suggested, including in epilepsy, innate fear, pain, and cardiac remodeling, but limitations in tools to probe these channels have restricted progress. A key question is whether we can overcome these limitations and develop tools that are high-quality, reliable, easy to use, and readily accessible for all investigators. Here, through chemical synthesis and studies of native and overexpressed channels by Ca^{2+} and patch-clamp assays, we describe compound 31, a remarkable small - molecule inhibitor of TRPC1 / 4 / 5 channels . Its potency ranged from 9 to 1300 pM, depending on the TRPC1 / 4 / 5 subtype and activation mechanism. Other channel types investigated were unaffected, including TRPC3, TRPC6, TRPV1, TRPV4, TRPA1, TRPM2, TRPM8, and store-operated Ca^{2+} entry mediated by Orai1. These findings suggest identification of an important experimental tool compound, which has much higher potency for inhibiting TRPC1 / 4 / 5 channels than previously reported agents, impressive specificity, and graded subtype selectivitywithintheTRPC1/ 4 /5channelfamily.Thecompoundshould greatly facilitate future studies of these ion channels . We suggest naming this TRPC1 / 4 / 5 -inhibitory compound Pico1 4 5 .

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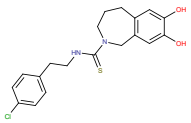
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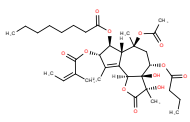
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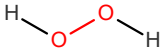
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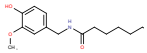
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MeSH
Calcium; Calcium Channel Blockers; HEK293 Cells; Humans; ORAI1 Protein; TRPC Cation Channels

Engineering controlled terms
Cell membranes; Electrophysiology; Mammals; Molecules

EMTREE drug terms
calcium ion; calcium release activated calcium channel 1; compound 31; ion transport affecting agent; transient receptor potential channel 1; transient receptor potential channel 3; transient receptor potential channel 4; transient receptor potential channel 5; transient receptor potential channel 6; transient receptor potential channel A1; transient receptor potential channel M2; transient receptor potential channel M8; unclassified drug; vanilloid receptor 1; vanilloid receptor 4; calcium; calcium channel blocking agent; calcium release activated calcium channel 1; ORAI1 protein, human; transient receptor potential cation channel, subfamily C, member 1; transient receptor potential channel C; TRPC4 ion channel; TRPC5 protein, human

Engineering uncontrolled terms
Activation mechanisms; Cardiac remodeling; Cationic channels; Cell functions; Mammalian cells; Small molecule inhibitor; Small molecules; Transient receptor potentials

EMTREE medical terms
antagonist potency; Article; chemical structure; controlled study; endothelium cell; human; human cell; patch clamp technique; priority journal; protein synthesis inhibition; synthesis; antagonists and inhibitors; chemistry; genetics; HEK293 cell line; metabolism

Engineering main heading
Synthesis (chemical)

Topic cluster
Stromal Interaction Molecule 1; Calcium Release Activated Calcium Channels; TRPC6 Cation Channel

Prominence percentile
98.49388

calcium ion
14127-61-8
vanilloid receptor 1
363242-41-5
calcium
7440-70-2, 14092-94-5
Calcium
Calcium Channel Blockers
ORAI1 Protein
ORAI1 protein, human
transient receptor potential cation channel, subfamily C, member 1
TRPC Cation Channels
TRPC4 ion channel
TRPC5 protein, human

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