Diaryl Borinic Acids Modulate Store-operated Calcium Entry (SOCE)

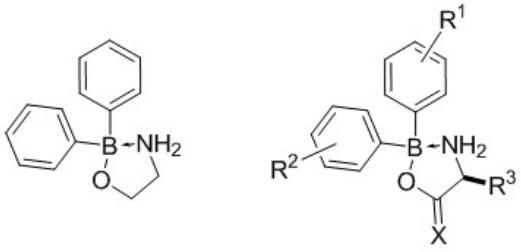
A. Schild[1], R. Bhardwaj[2], M. A. Hediger[2], M. Lochner[1,2]*

[1]Department of Chemistry and Biochemistry, [2]Institute of Biochemistry and Molecular Medicine

The intracellular Ca^{2+} concentration is carefully controlled, as changes in $[Ca^{2+}]_i$ mediates a plethora of cellular and ultimately physiological processes, such as cell differentiation, muscle contraction, neurotransmission, proliferation and immune cell mobility, among many others.

Intracellular Ca^{2+} is stored in the endoplasmic reticulum (ER) and released upon activation of ER-receptors (e.g. IP_3). Refilling of the ER Ca^{2+} stores requires an intricate interplay and assembly between Ca^{2+} sensing proteins (STIM1 and STIM2) located in the ER membrane and proteins (Orai1, 2 and 3) in the plasma membrane. The resulting STIM/Orai complexes form a Ca^{2+} channel that causes a measurable calcium-release activated calcium current (I_{CRAC}). Mutations in STIM or Orai that either cause enhanced or reduced store-operated calcium entry (SOCE) have been associated with muscular and immunodeficiency diseases, respectively.

Diphenyl borinate 2-APB (**1**) exhibits a dual function on SOCE, as it blocks at high concentration (e.g. 50 µM) but potentiates SOCE at lower concentrations (e.g. 5 µM). In this work, we present the synthesis of novel 2-APB analogues (**2**), some of their crystal structures and their concentration-dependent influence on SOCE. Specifically, we have investigated Orai-subtype selectivity (Orai1 vs. Orai3) and have also generated some fluorescent 2-APB congeners.



1: 2-APB **2**: X = H_2 or O

[1] M. Prakriya, R. S. Lewis, *Physiol. Rev.*, **2015**, *95*, 1383-1436.!
[2] A. Hofer, G. Kovacs, A. Zappatini, M. Leuenberger, M. A. Hediger, M. Lochner, *Bioorg. Med. Chem.*, **2013**, *21*, 3202-3213.