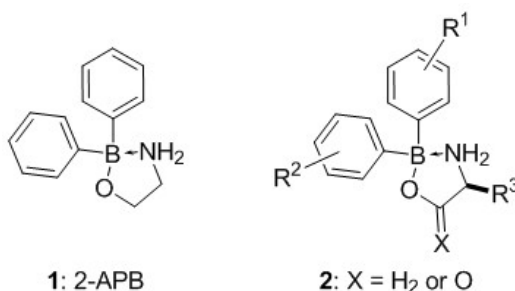


**Diaryl Borinic Acids Modulate Store-operated Calcium Entry (SOCE)**A. Schild<sup>1</sup>, R. Bhardwaj<sup>2</sup>, M. A. Hediger<sup>2</sup>, M. Lochner<sup>1,2\*</sup><sup>1</sup>Department of Chemistry and Biochemistry, <sup>2</sup>Institute of Biochemistry and Molecular Medicine

The intracellular  $\text{Ca}^{2+}$  concentration is carefully controlled, as changes in  $[\text{Ca}^{2+}]_i$  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  $\text{Ca}^{2+}$  is stored in the endoplasmic reticulum (ER) and released upon activation of ER-receptors (e.g.  $\text{IP}_3$ ). Refilling of the ER  $\text{Ca}^{2+}$  stores requires an intricate interplay and assembly between  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  channel that causes a measurable calcium-release activated calcium current ( $I_{\text{CRAC}}$ ). 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.  $50 \mu\text{M}$ ) but potentiates SOCE at lower concentrations (e.g.  $5 \mu\text{M}$ ). 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] 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.