N-(p-Amylcinnamoyl)anthranilic acid (ACA) is a modulator of various ion channels in the heart. ACA is an effective reversible inhibitor of calcium-activated chloride channels and, to a lesser extent, cAMP-activated chloride channels, without affecting L-type calcium channels.[2] Calcium-activated chloride channels are believed to be involved in developing arrhythmia.[2][3]

The transient receptor potential melastatin 2 (TRPM2) channel is associated with ischemia reperfusion injury, inflammation, cancer, and neurodegenerative diseases. However, the limit of specific inhibitors impedes the development of TRPM2-targeted therapeutic agents. To discover more potent and selective TRPM2 inhibitors, 59 N-(p-Amylcinnamoyl)anthranilic acid (ACA) derivatives were synthesized and evaluated using calcium imaging and electrophysiology approaches. Systematic structure-activity relationship studies resulted in some potent compounds inhibiting the TRPM2 channel with sub-micromolar half-maximal inhibitory concentration values. Among them, the preferred compound A23 exhibited TRPM2 selectivity over TRPM8 and TRPV1 channels as well as phospholipase A2 and showed neuroprotective activity in vitro. Following pharmacokinetic studies, A23 was further evaluated in a transient middle cerebral artery occlusion model in vivo, which significantly reduced cerebral infarction. These data indicate that A23 might serve as a useful tool for TRPM2-related research as well as a lead compound for the development of therapeutic agents for ischemic injury [1].

1)
Zhang H, Yu P, Lin H, Jin Z, Zhao S, Zhang Y, Xu Q, Jin H, Liu Z, Yang W, Zhang L. The Discovery of Novel ACA Derivatives as Specific TRPM2 Inhibitors that Reduce Ischemic Injury Both In Vitro and In Vivo. J Med Chem. 2021 Mar 30. doi: 10.1021/acs.jmedchem.0c02129. Epub ahead of print. PMID: 33784097.