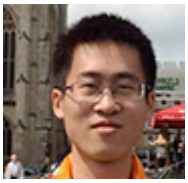
Valinomycin for chloride: Nonprotonophoric electrogenic chloride carriers



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Valinomycin is a naturally occurring depsipeptide that functions as a transmembrane K^+ carrier without facilitating H^+/OH^- transport.[1] Synthetic anion carriers that selectively facilitate Cl^- transport without H^+/OH^- transport ("valinomycin for chloride") have potential as tools for biomedical research and as therapeutic agents for diseases associated with anion-channel dysfunction such as cystic fibrosis.[2] Despite research efforts in the development of synthetic anion carriers,[3] the possibility of H^+/OH^- transport has received little attention, and an anionophore proven to be selective for Cl^- over H^+/OH^- is currently unavailable. Here, we show that depending on anionophore acidity, many anionophores facilitate H^+ or OH^- transport, potentially leading to toxicity. To address this problem, we developed two new small molecules that promote Cl^- transport without effectively dissipating the transmembrane pH gradient, mimicking the ion conducting function as valinomycin. The Cl^- > H^+/OH^- selectivity of anionophores showed a consistent positive correlation with the degree of Cl^- encapsulation and a negative correlation with the acidity of hydrogen-bond donors. Our study demonstrates that a valinomycin equivalent for Cl^--selective transport is achievable.[4]

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