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## **Mechanistic Studies of the GYKI Compounds**

Excessive activation of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) subtype of ionotropic glutamate receptors has been implicated as a leading contributor to a number of neurological diseases, such as epilepsy, stroke and amyotrophic lateral sclerosis (ALS). Using inhibitors as neuroprotective drugs to dampen the excessive receptor activity has been a long pursued therapeutic strategy. 2,3-Benzodiazepine derivatives, also known as GYKI compounds, are inhibitors of AMPA receptors, and they represent a class of the most promising drug candidates developed to date. However, the quantitative, functional activities of these compounds on AMPA receptors remain poorly defined. This is because AMPA receptors open their channels in the microsecond time domain and desensitize even in the millisecond time region. Yet, current kinetic techniques do not have sufficient time resolutions required to characterize the kinetic mechanism of channel opening and the mechanism of inhibitor/drugreceptor interaction.

In this proposal, we will systematically elucidate the mechanism of action for a series of 19 GYKI compounds, measure their potency on specific AMPA receptor subunits, and characterize the structure-activity relationship, including the number of inhibitory sites on a receptor and whether any two sites interact with each other (i.e., the binding of two inhibitors to their sites can be independent or negatively affected by binding of either one first). To achieve the specific aims, we will carry out a number of experiments, including a laserpulse photolysis study with the  $\mu$ s time resolution to investigate the effect of a GYKI compound on the channel-opening rate process of an AMPA receptor. The kinetic investigation of these compounds, relevant to the time scale within which all receptor forms are still functional, has not been previously possible. Our results on the receptor properties and the structure-activity relationship of these compounds will be valuable for rational design and synthesis of subunitand conformation-selective GYKI compounds with higher potency so that AMPA receptor activities can be controlled more quantitatively.