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Initial SAR studies on apamin-displacing 2-aminothiazole blockers of calcium-activated small conductance potassium channels

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ABSTRACT

An initial SAR study on a series of apamin-displacing 2-aminothiazole $K_{Ca}2$ channel blockers is described. Potent inhibitors such as *N*-(4-methylpyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (**13**) are disclosed, and for select members of the series, the relationship between the observed activity in a thallium flux, a binding and a whole-cell electrophysiology assay is presented.

Small conductance calcium-activated potassium (K_{Ca}) channels are expressed predominately in neuronal cells.[1] They are voltage insensitive and open in response to elevated concentrations of intracellular calcium. Calcium ions bind to calmodulin, a protein that is constitutively associated with the C-terminal domain of the K_{Ca} channel. This protein modulates the state of the channel in response to its calcium occupancy, whereby higher occupancy is associated with opening of the channel.[2–6] K_{Ca} channel opening results in hyperpolarization of the plasma membrane[7] with a concomitant reduction in neuronal excitability. The hyperpolarization phenomenon (termed an afterhyperpolarization or AHP) can persist for several hundreds of milliseconds,[8] and significantly affects the rate and pattern of neuronal firing.[9,10]

Three isoforms of K_{Ca} channels have been identified and cloned: $K_{Ca}2.1$, $K_{Ca}2.2$ and $K_{Ca}2.3$. In situ hybridization, Northern blot, and RT-PCR studies have demonstrated differential regional expression levels of the isoforms in both rat and human brain.[1,9,11,12]

Correspondingly, there exists the possibility for site selective modulation of neuronal excitability if suitable pan-K_{Ca} or sub-type selective K_{Ca} channel modulators can be identified. Such agents may have utility in the treatment of a number of pathological conditions[13] including epilepsy, depression, and Parkinson's disease,[14] as well as schizophrenia.[15] They may also prove helpful in treating certain cognitive disorders.[16,17]

A limited number of compounds have been reported to be active at K_{Ca} channels. The cyclic octapeptide apamin is a highly selective and potent blocker with reported IC_{50}'s between 30 pM and 20 nM.[1,18] The larger peptide Scyllatoxin is exceptionally potent (K_i = 75 pM)[19,20] and related derivatives display moderate selectivity among the K_{Ca} channel subtypes. As shown in Figure 1 above, dequalinium (IC_{50} = 1.0 μM) was the first non-peptidic K_{Ca} selective blocker identified.[21] Subsequent development of this chemotype led to the discovery of the cyclophane derivative, UCL 1684, a compound that displayed similar potency to apamin (IC_{50} = 3.0 nM).[22] More recently, quinoline appended diazepines[23] (K_i = 140 nM) and isoquinoline analogs related to bicuculline and *N*-methyl laudanosine[24–28] have been reported, as well as the non-apamin displacing 2-aminobenzimidazoles, such as NS8593 (IC_{50} = ~500 nM).[29] In this Letter, we describe a preliminary SAR study on a series of aminothiazoles that display significant K_{Ca} channel activity. In addition, we confirm the previously reported activities of some of these analogs[30] in alternative assay systems, and significantly expand on reported selectivity and mechanism of inhibition studies.

The thiazole chemotype discussed here was identified from a high-throughput screen that employed a thallium flux assay,[33] in which compounds were tested against a HEK 293 cell line recombinantly expressing specific K_{Ca} channel isoforms. Several chemotypes were identified with one of the more interesting being the 2-aminothiazole derivative **1**, as shown in Figure 2.

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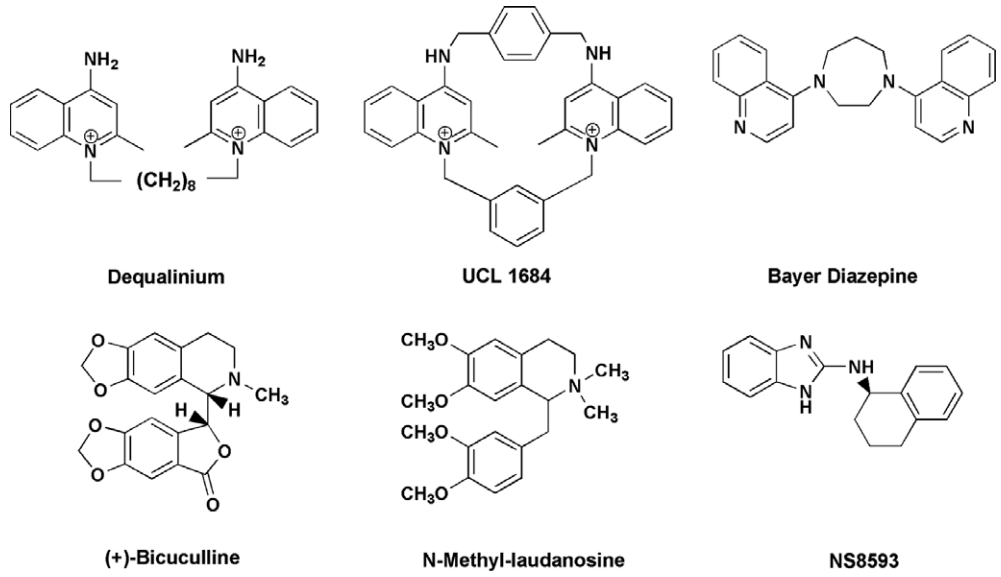

Figure 1. Examples of reported, non-peptidic blockers of K_{Ca} channels.

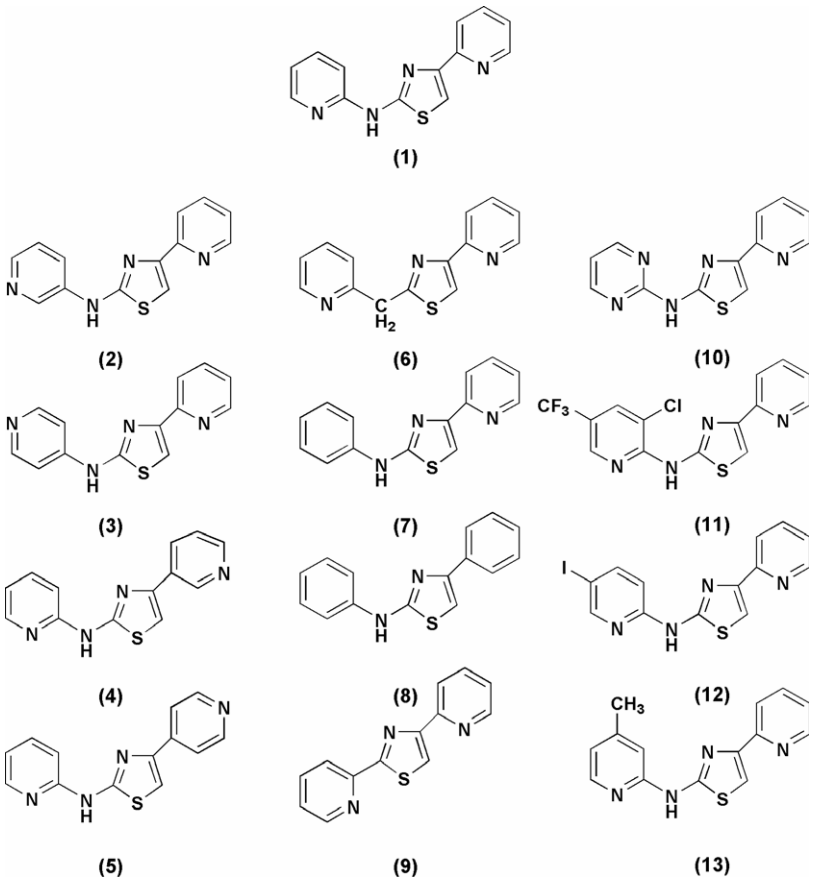

Figure 2. Aminothiazoles evaluated for activity at K_{Ca} channels.

This compound displayed significant potency (89% inhibition at 30 μM) in the original screen. It was resynthesized, and its IC_{50} in the thallium assay was determined to be 0.5 μM. In a subsequent whole-cell electrophysiology experiment, the IC_{50} of **1** was found to be in close agreement with the value obtained in the thallium assay, as shown in Table 1. In addition to the compound's impressive activity, we anticipated that its physicochemical properties [M_W = 254, *C*Log*P* = 2.71, HBD = 1, HBA = 3, ACD pK_a (conjugate acid) = 3.8] held excellent promise for its advancement and utility in investigating CNS effects of K_{Ca} channel block.

Subsequently, we investigated the activities of the series of related aminothiazoles shown in Figure 2. These compounds are either commercially available, or can be synthesized from readily accessible starting materials using the methodology depicted in