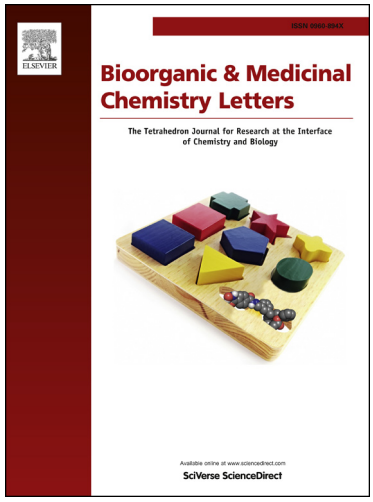

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ABSTRACT

A novel class of $Na_V1.7$ inhibitors has been identified by high-throughput screening followed by structure activity relationship studies. Among this series of compounds, piperidine **9o** showed potent human and mouse $Na_V1.7$ inhibitory activities with fair subtype selectivity over $Na_V1.5$. Compound **9o** successfully demonstrated analgesic efficacy in mice comparable to that of the currently used drug, mexiletine, but with an expanded central nervous system safety margin.

Since pain is known as the most common symptom reported by almost all patients, there are still huge unmet medical needs with regard to treating it. Genetic analysis of congenital insensitivity to pain (CIP) patients revealed that the loss of SCN9A gene function leads to CIP, and the SCN9A gene has been shown to encode voltage-gated sodium channel 1.7 ($Na_V1.7$).[1] On the other hand, the gain of SCN9A gene function was shown to be involved in a wide spectrum of human genetic pain disorders.[2] Moreover, deletion of the SCN9A gene in both sensory and sympathetic neurons in mice is known to result in the same phenotype as in humans.[3] In fact, several Na_V blockers, such as lidocaine (**I**) and mexiletine (**II**) (Figure 1), have been used clinically to treat various types of pain disorder. Consequently, $Na_V1.7$ inhibitors are expected to be promising analgesic agents. Herein, we report the discovery and structure activity relationship of novel $Na_V1.7$ inhibitors with several biological properties.[4]

Through the high-throughput screening (HTS) of our corporate library, piperazine derivative **1** was identified (Figure 1).[5] When *in vitro* evaluations of $Na_V1.7$ inhibitory activity were performed, the inhibitory activities of $Na_V1.1$ and $Na_V1.5$ were also evaluated because inhibiting $Na_V1.1$ is known to cause central nervous system (CNS) side effects such as dizziness and sedation, whereas the inhibition of $Na_V1.5$ leads to cardiac arrhythmias.[6] HTS hit **1** inhibited $Na_V1.7$ at IC_{50} = 3.9 μM with fair subtype selectivity over $Na_V1.1$ and $Na_V1.5$ (over 8.5-fold and 5.1-fold, respectively). Therefore, to acquire potent and highly subtype-selective $Na_V1.7$ inhibitors, the derivatization of HTS hit **1** was commenced.

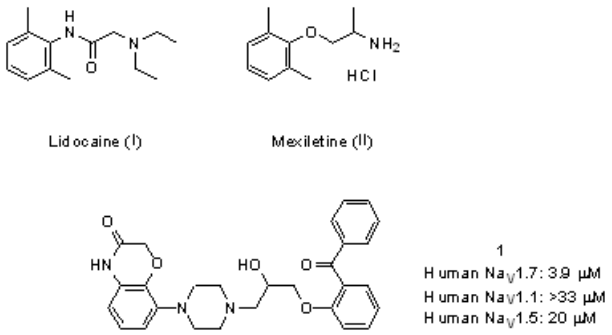

Figure 1. The structures of lidocaine (**I**), mexiletine (**II**) and HTS hit **1** with human Na_V IC_{50} values.

Initial studies were focused on the conversion of benzoxazinone and piperazine moieties, as shown in Table 1. For a reference, the *in vitro* profile of mexiletine (**II**) was acquired to confirm that mexiletine (**II**) is a non-selective weak Na_V inhibitor.