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Abstract

New TRPV1 Antagonists as Candidates for Effective Anticonvulsant and Antinociceptive Agents †

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Abstract: Epilepsy is recognized as one of the most common neurological disorders with a high risk of drug resistance. Notably, about one-third of the patients with epilepsy are not responsive to pharmacological treatment. Thus, the search for new, more effective anticonvulsants with a novel mechanism of action is undoubtedly necessary. The most recent neurobiological studies implicate central TRPV1 receptors in the induction of epileptic seizures. Moreover, it is suggested that TRPV1 desensitization is one of the crucial mechanisms of action responsible for the anticonvulsant activity of cannabidiol (CBD), which was proven to be effective against drug-resistant epilepsy. Bearing in mind the aforementioned facts, we developed in our recent studies a series of chemically original TRPV1 antagonists. Their structures were designed as integrated hybrids that join on the common chemical template the structural fragments of anticonvulsants identified by our team in the previous studies and known TRPV1 antagonists (described in the literature). As a result, these compounds revealed potent anticonvulsant activity in the preclinical studies using the most widely employed animal seizure models, namely, the maximal electroshock (MES) test, and the psychomotor 6 Hz (32 mA and 44 mA) seizure model in mice. In addition, selected substances demonstrated potent effectiveness by decreasing pain responses in formalin-induced tonic pain, in capsaicin-induced neurogenic pain, as well as in oxaliplatin-induced neuropathic pain in mice.

Keywords: TRPV1 antagonists; anticonvulsant activity; antinociceptive activity; hybrid compounds

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