Discovery and Profiling of a Peripherally-restricted GABA-A Positive Allosteric Modulator for Treatment of Irritable Bowel Syndrome

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A new class of therapeutic compounds has been developed for the treatment of pain and motility associated with irritable bowel syndrome (IBS) by selectively targeting GABA-A receptors in the enteric nervous system. The benzodiazepine class of drugs modulate GABA-A receptors and are important therapeutics for many CNS conditions such as anxiety, epilepsy, and insomnia. These drugs (e.g. Valium) readily cross the blood brain barrier and act via central modulation of GABA-A receptors. To date, they have not shown useful efficacy in treatment of peripheral pain states, most likely due to dose-limiting somnolence/sedation. Disclosed herein are a class of closely-related compounds that do not pass the blood-brain barrier, and therefore can exploit peripheral GABA-A receptors for treatment of pain without CNS side effects. This strategy is similar to the utility of non-sedating antihistamines for treatment of allergy/inflammation which are also peripherally-restricted. Based on the extensive structure-activity relationships developed for the benzodiazepine class of compounds, novel molecules containing polar functional groups were designed and prepared. Potent binding compounds were profiled across 6 subtypes of GABA-A receptors to identify pure positive allosteric modulators (PAMs) similar to classical benzodiazepines. Extensive ADME profiling demonstrated good overall pharmacokinetics but poor brain penetration, and a lead compound demonstrated efficacy in models of IBS.