PHARMACOLOGICALLY-ACTIVE VANILLOID CARBAMATES

Published date: Feb. 6, 2014

Technology description

Invention Summary:
Inflammation, often treated with steroidal and non-steroidal anti-inflammatory drugs (NSAIDs), is inherent in the many clinical conditions and topical diseases. These include, but are not limited to dermal abrasions, psoriasis, arthritis, multiple sclerosis, Alzheimer’ s disease, depression, amyotrophic lateral sclerosis, dementia, Parkinson’ s disease, and other neurodegenerative states. The enzyme fatty acid amide hydrolase (FAAH) and the transient receptor potential vanilloid (TRPV1) are two of several drug targets to treat inflammatory clinical conditions.The endocannabinoid system is well-characterized to be a key lipid signaling pathway in inflammation, pain control, neurological diseases, and fat metabolism. An enzyme known to degrade endocannabinoids is FAAH. Inhibitors of this enzyme prevent degradation of endocannabinoids and other fatty acid amides. While increased levels of these mediators may be beneficial, the FAAH inhibitors are likely to possess therapeutic value.Recently, the inhibition of FAAH has been implicated as a pre-screen for pharmaceuticals for anti-inflammatory effects, pain suppression, and neuropsychiatric disorders. Among other structures, alkyl carbamates are known to be potent FAAH inhibitors and candidate therapeutics. Another target also closely linked to modulation of pain and inflammation is TRPV1.TRPV1 is a non-selective cation channel that may be activated by a wide variety of physical and chemical stimuli, such as heat, vanilloids and small molecule amides. Unlike traditional analgesic drugs that either suppress inflammation (e.g., NSAIDs and COX-2 inhibitors) or block pain transmission (e.g., opiates), TRPV1 channel inhibitors aim to prevent pain and inflammation by blocking a receptor where these adversities are generated.A new class of pro-drugs, vanilloid carbamates, has been prepared with three novel synthetic procedures. One of which (Method C) is especially-suited for parallel syntheses. These vanilloid carbamates were tested positive as FAAH inhibitors and TRPV1 modulators.Usingthe mouse ear inflammation model,these vanilloid carbamates are also proven to be anti-inflammatory agentsin vivo. Thevanilloid carbamateswere applied to the ears prior to inflammatory agent treatment. For two inflammation-inducing agents (TPA and CEES) tested, the vanilloid carbamates were shown being able to greatly suppress inflammation in both cases.

Application area

Drugs for anti-inflammatory activity
Drugs inhibiting FAAH and/or regulate TRPV1
Synthesis protocol of this series of new drugs
United States Patent Number 8,343,971 granted on January 1, 2013

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