Bioavailable Dual sEH/PDE4 Inhibitor for Inflammatory Pain

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Technology description

Soluble epoxide hydrolase (sEH) is an enzyme that metabolizes endogenous cytochrome P450s (CYP450) derived epoxy-fatty acids (EpFAs). Inhibition of sEH elevates EpFA levels, which has anti-hypertensive, anti-inflammatory, and analgesic properties. In general, however, the bioavailability of potent sEH inhibitors is poor while efforts to improve pharmacokinetics results in decreased potency. Phosphodiesterase 4 (PDE4) is an enzyme involved in the inflammatory response in immune cells and is a major target for inflammatory diseases such as psoriasis, psoriatic arthritis, chronic obstructive pulmonary diseases, and asthma. PDE4 activation is also correlated with symptoms of neuronal disorders such as depression, schizophrenia and Alzheimer’ s disease. Currently, PDE4 Inhibitors are used to block the PDE4 enzyme in inflammatory pain therapies but have limited use due to side effects such as nausea and vasculitis.

Researchers at the University of California, Davis, have developed a new drug that inhibits both soluble epoxide hydrolase (sEH) and phosphodiesterase 4 (PDE4). This drug has been shown to reduce inflammatory pain in rats after oral application. Co-administration of PDE4 and sEH inhibitors resulted in an enhanced analgesic effect compared to the individual treatment and, by inhibiting both enzymes, the new sEH/PDE4 dual compound has the potential to provide rapid relief of inflammatory pain while improving bioavailability, mitigating vasculitis and limiting side effects such as nausea. Additionally, based on the current knowledge of the involved single targets and their inhibitors, diseases such as hypertension, COPD, neuropathic pain and depression could also potentially be addressed by this compound.

Related Materials

Blöcher, René et al. “Orally Available Soluble Epoxide Hydrolase/Phosphodiesterase 4 Dual Inhibitor Treats Inflammatory Pain.” Journal of Medicinal Chemistry. EPub 03 Apr 2018. doi: 10.1021/acs.jmedchem.7b01804.

Application area

Inflammatory diseases such as psoriasis, psoriatic arthritis, chronic obstructive pulmonary diseases, and asthma

Neuropathic pain

Hypertension
Depression

Advantages

Orally bioavailable
Synergistic analgesic effect
Potent dual ligands with IC_{50} values ranging from subnano to submicromolar concentrations

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