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A New Family of Subnanomolar inhibitors of Soluble Epoxide Hydrolase

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Abstract

The pharmacological inhibition of soluble epoxide hydrolase (sEH) has been suggested as a potential therapy for the treatment of pain and inflammatory diseases through the stabilization of epoxyeicosatrienoic acids, endogenous chemical mediators derived from arachidonic acid that show anti-inflammatory and analgesic effects.[1]

Although several potent sEH inhibitors (sEHI) have been developed, including clinical candidates AR9281, GSK2256294, and EC5026, so far no sEHI has reached the market.[2]

Recently, a new series of benzohomoadamantane-based ureas endowed with potent inhibitory activity for the human and murine sEH was reported. However, their very low microsomal stability prevented further development.[3]

Herein, novel series of benzohomoadamantane-based ureas were synthesized, fully characterized, and evaluated as sEHI. Most of them were endowed with subnanomolar inhibitory potencies at the human and murine enzymes. Further in vitro profiling (solubility, cytotoxicity, metabolic stability, CYP450s, hLOX-5, hCOX-2, hERG inhibition, permeability) allowed us to select a candidate for efficacy studies.

In summary, these novel results and the previously reported studies using other families of sEHI, strongly suggest that sEH may be a target of clinical interest for the treatment of inflammatory and pain-related disorders.[4]

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