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Extended Abstract

Adamantane Analogs: From Anti-Influenza Drugs to Soluble Epoxide Hydrolase Inhibitors for Acute Pancreatitis †

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† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 7 August 2019

Keywords: acute pancreatitis; adamantane; influenza; M2 channel; medicinal chemistry; soluble epoxide hydrolase

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The adamantane scaffold is present in eight approved drugs. It is also featured in several compounds in clinical trials [1]. However, ring-contracted, ring-expanded or heteroanalogs of adamantane have been largely ignored in medicinal chemistry.

Soluble epoxide hydrolase (sEH) is an enzyme involved in the inflammatory pathway, which converts epoxyeicosatrienoic acids (EETs), endogenous chemical mediators derived from arachidonic acid, to their corresponding dihydroxyeicosatrienoic acids. Taking into account that EETs show very potent anti-inflammatory and analgesic properties, it has been proposed that inhibition of sEH may have therapeutic effects in various inflammatory diseases [2].

In this context, several adamantane-based potent sEH inhibitors have been developed, but their low solubility and poor pharmacokinetic profiles have hampered their progress into clinics [3].

Herein, we will present: (a) The design and synthesis of several sEH inhibitors featuring an oxaadamantane moiety in order to improve the potency and pharmacokinetic profiles of previously studied adamantane-derived sEH inhibitors, (b) the screening cascade as well as the in vitro proof of concept (PoC) for selecting a candidate for in vivo studies, and (c) two in vivo PoC in which our candidate reduced inflammation and endoplasmic reticulum stress markers in murine models of cerulein-induced acute pancreatitis (AP).

Of note, AP is a serious and life-threatening inflammatory disease and arises as one of the most common gastrointestinal disorders worldwide. Aside from palliative treatments (analgesics, hydration, antibiotics), there is no standard therapeutic strategy for reducing inflammation in AP.

References

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