UNIVERSITÄT LEIPZIG

Stable inhibitors of the 5-lipoxygenase pathway for treating asthma and cancer

IDEA

Introduction of metabolically stable carboranes into inhibitors of the 5-LO pathway to enhance the pharmacokinetic profile of related drugs.

DEMONSTRATOR

Introduction of carboranes maintains the inhibitory potential for 5-LO, but the cytotoxicity for invasive melanoma and colon cancer cell lines is strongly increased. IC_{50}= 10-20 µ molar

ANIMAL STUDIES

Mice with colon denocarcinoma show an improved response to the investigated compounds (clear reduction of tumour). No acute toxicity.

CLINICAL STUDIES

We are looking for cooperation partners to carry out preclinical and clinical studies.

BACKGROUND/ MEDICAL PROBLEM

5-Lipoxygenase (5-LO) is an enzyme that catalyses the conversion of arachidonic acid to biologically active leukotrienes (LTs). LTs are cellular signalling mediators involved in inflammatory diseases, such as asthma, atherosclerosis, cardiovascular diseases and diverse types of cancer, e.g. acute myeloid leukaemia. Competitive LT receptor antagonists such as *montelukast* and zafirlukast have been developed to decrease the symptoms of an overexpression of LTs. They bind to the cysteinyl leukotriene receptor (CysLT1), which is disadvantageous, since lipoxygenases also produce other LTs that bind to other receptors. Therefore, the inhibition of 5-LO is beneficial, since the production of all LTs is decreased. *Zileuton* for treatment of asthma is the only drug on the market inhibiting the 5-LO pathway. However, the pharmacological profile of zileuton is disadvantageous, since it is rapidly metabolised.

POTENTIAL APPLICATION

- Treatment of 5-LO dependent tumours
- Tumour imaging
- Boron neutron capture therapy (BNCT)

BENEFITS

- 5-Lipoxygenase is a therapeutic target involved in diseases like asthma, atherosclerosis and cancer
- Carboranes improve pharmacokinetic behaviour
- Carborane-based 5-LO inhibitors increase the selective cytotoxicity for cancer cells
- Easy and fast synthesis in three steps

Project 17008

TECHNOLOGY OFFER

Picture: Colourbox

Carborane-based 5-LO inhibitors

TECHNOLOGY/SOLUTION

We have investigated the substitution of metabolisable phenyl rings of lipoxygenase inhibitors by metabolically stable boron compounds, namely, carboranes ($C_2B_{10}H_{12}$). Carboranes are icosahedral boron clusters in which two boron atoms are replaced by carbon atoms. They are non-toxic, have remarkable biological stability, and the carbon atoms can be functionalised easily and selectively. We have found that the introduction of carboranes does not influence the inhibitory potential for the 5-LO pathway, but strongly and selectively increases the cytotoxicity for cancer cells.

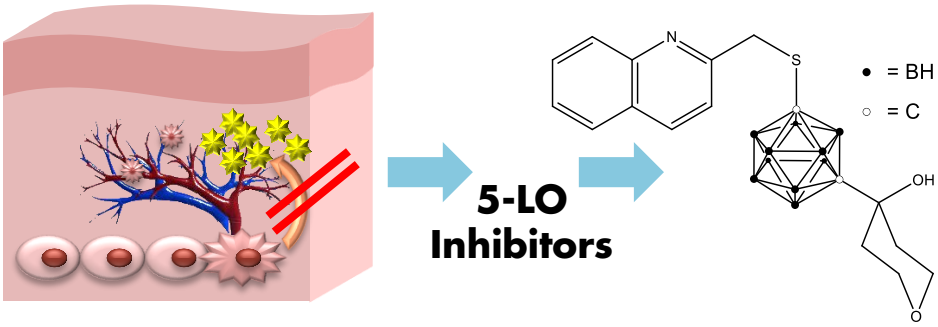

Figure
Left: Leukotrienes, produced by 5-lipoxygenase, lead to angiogenesis and metastasis of cancer cells.
Right: Introduction of carboranes leads to highly selective and metabolically stable lipoxygenase inhibitors which can prevent angiogenesis.

FURTHER READING

J. Roos et al., Pharmacol. Ther., 2016, 157, 43–64.

O. Werz, Planta Med., 2007, 73, 1331–1357.

STATUS OF PROPRIETARY RIGHTS

Patent is pending
PCT 00401P0085WO

COOPERATION OPTIONS

- R&D Agreement
- License Agreement
- Ownership Agreement

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