

5-thiohistidine compounds and methylated derivatives (ovothiols) as inhibitors of gamma-glutamyl-transpeptidase (GGT) activity



Abstract

The invention relates to the use of a class of modified sulphur-containing amino acids called 5-thiohistidines and their methylated derivatives (ovothiols) as inhibitors of the cell membrane enzyme gamma-glutamyl transpeptidase (GGT) and their use for the prevention and treatment of diseases related to high expression and activity of GGT.

State of the art

5-thiohistidines and the analogous methylates are natural molecules of marine origin, which are found in millimolar quantities in the eggs of sea urchins, holothurians and various types of molluscs such as clams, scallops and mussels. They are also produced by certain strains of bacteria and microalgae. A chemical synthesis protocol for the unmethylated precursor has also been described, while the methylated derivatives are obtained by biosynthesis from bacteria and engineered microalgae. GGT, on the other hand, is an enzyme present on the cell membrane of various tissues and in particular in large quantities in organs such as the liver and the kidney. Its production and activity can increase in various diseases involving the inflammation and malfunctioning of these organs. In these conditions, GGT is also released into the bloodstream in excessive amounts, making it a diagnostic marker.

Invention Description

The use of GGT inhibitors represents a valuable support for the therapy of diseases related to its excessive production and activity. For example, GGT inhibitors are used as adjuvants for the treatment of GGT over-expressing tumours that are particularly resistant to chemotherapy. However, already known and marketed inhibitors have presented several toxic side effects so they have been abandoned at different stages of clinical trials.

With this patent, the authors describe the use of 5-thiohistidines and the analogous methylates as more potent and toxicity-free inhibitors of GGT activity than those already known, and the use of these molecules in the treatment of diseases related to high GGT activity, such as liver fibrosis.

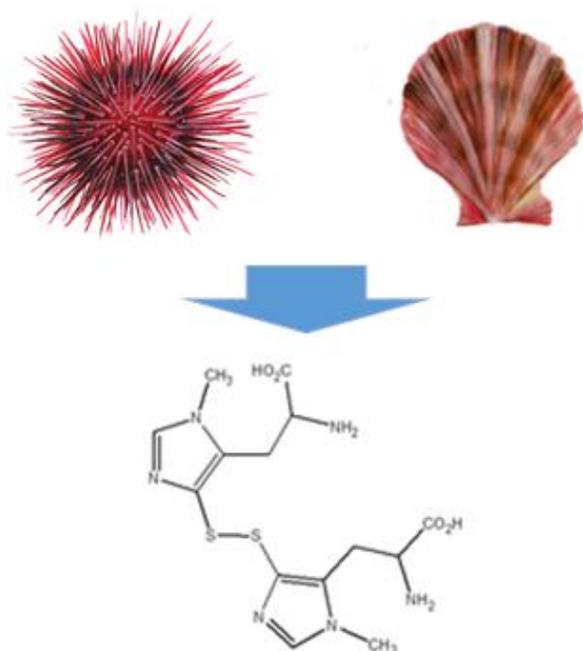


FIGURE 1 – Ovothiols and marine source*

*Pictures of Flora Palumbo

Industrial Property

European Patent Application no. 19210282.0 filed with priority on 11/20/2019

Italian Patent granted with no. 102018000010907 and filed on 10/12/2018

Applicant

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Advantages

The advantages of this patent are the following:

- this class of compounds proves to be more effective (IC50 around 20 μM) than existing inhibitors with at least 10 times the potency;
- these molecules show no toxicity on cells *in vitro* at least up to a dose of 200 μM ;
- the efficacy of these compounds was tested on *in vivo* models of mice with liver fibrosis, a pathology related to high levels of GGT.
- the administration of these molecules significantly induced the reduction of GGT activity and other markers of liver fibrosis, as well as of collagen fibres deposited in the matrix of the liver tissue of mice with liver fibrosis (Fig. 2).

Applications

This patent finds application in the following areas:

- Scientific Research - into systems for determining GGT activity and induced mechanisms;
- Pharmaceutical and Nutraceutical markets - for the use of 5-thiohistidines and their derived methylates for the prevention and treatment of diseases associated with high GGT activity (liver diseases such as liver fibrosis, reperfusion ischaemia, certain respiratory diseases).

Development stage

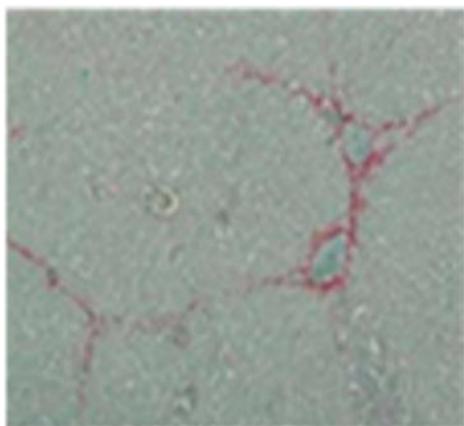
Current TRL: 4

We are in the preclinical phase. In order to evaluate the efficacy of the invention, experimental phases have been conducted *in vitro* on cultured over-expressing GGT cells and *in vivo* on mouse models of liver fibrosis.

Perspective TRL: 5

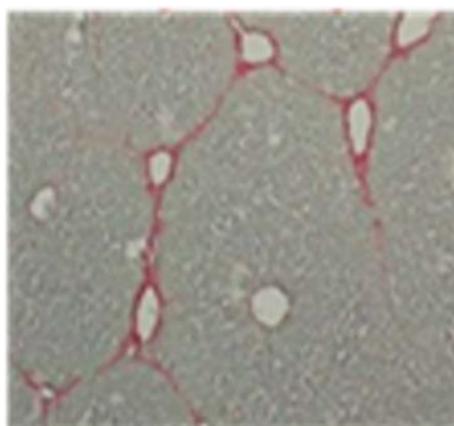
Pilot lots will be produced for further development; safety and toxicity studies will be performed in animal model systems.

Liver histology



Treatment with ovothiols reduces the collagen fibres (coloured in red) deposited in the liver tissue

Liver histology



Untreated fibrotic liver tissue (red-coloured collagen fibres)

FIGURE 2 – Effect of treatment with ovothiols in the animal models with liver fibrosis (such as GGT – dependent disease)