CYSTEINE PROTEASE INHIBITORS WITH APPLICATIONS IN TROPICAL INFECTIOUS DISEASES

DESCRIPTION FO THE INVENTION

The Universitat Jaume I of Castelló (UJI) has developed and patented new compounds that show a powerful inhibitory activity against protease cysteine-type therapeutic targets, which makes them powerful drugs for use against tropical diseases such as sleeping sickness, Chagas disease or malaria, while they also display a low degree of toxicity. Cell trials show that the new chemical compounds selectively inhibit the development of the protozoa that cause these diseases in human cells.

Malaria, sleeping sickness, Chagas disease and leishmaniasis are the main parasitic pathologies in developing countries. They all give rise to huge amounts of damage in terms of human suffering and loss of life, and are a hindrance to the economic and social development of these territories.

Pharmaceutical research has still not come up with a definitive solution for this challenge faced by worldwide healthcare. The medicines that are currently used display either low effectiveness or undesirable side effects, and often both at the same time. Hence, there is an urgent need to find new drug products for these pathologies.

All the pathogenic agents causing these four tropical diseases exhibit a common enzymatic activity that is essential for their life cycle, namely, that carried out by the enzymes in the cysteine protease group, i.e. cruzain in the case of Trypanosoma cruzi (Chagas disease), rhodesain in the case of Trypanosoma brucei (sleeping sickness) and falcipain in the case of Plasmodium falciparum (malaria). These enzymes have been identified as therapeutic targets for these diseases.

It is therefore not surprising that recent research has focused on the search for compounds capable of inhibiting the action of these cysteine proteases, with the aim of blocking the natural life cycle of the protozoa and stopping the infection from advancing. The synthesis of inhibitors of these enzymes could give rise to new pharmaceuticals with which to combat malaria, Chagas disease and sleeping sickness, especially as an alternative to traditional therapies in resistant organisms.

To date, the strategy has yielded results that are not entirely satisfactory. For example, irreversible cysteine protease inhibitors based on peptides have been developed that have the disadvantage of being highly reactive, which makes them not very selective and, hence, very toxic. With the aim of increasing the selectivity and reducing the reactivity of these compounds, other less reactive molecules have been prepared, although they are penalised by not being effective in vivo due to their low bioavailability.

The technology presented here aims to overcome all these limitations. Accordingly, researchers at the UJI have designed and synthesised a family of a new type of chemical compounds that inhibit parasitic cysteine proteases very effectively. The inhibitors give the following values, expressed both as the IC50 values and as the quotient of the kinetic constants of the inhibitory process of the enzymes characterising each disease:

-Rhodesaína (Enfermedad del sueño)

k_{inact}/K_I = 1.610.000 $M^{-1}s^{-1}$

IC_{50} = 0,01635 µM

-Falcipain (Malaria)

k_{inact}/K_I = 28.200 $M^{-1}s^{-1}$

IC_{50} = 0,19 µM

-Cruzain (Chagas disease)

k_{inact}/K_I = 709.400 $M^{-1}s^{-1}$

IC_{50} = 0,0111 µM

The compounds were also tested against the human cysteine proteases known as cathepsins B and L, which also belong to the papain family. In some cases the IC_{50} values are similar to those of rhodesain, but in all cases the k_{inact}/K_I value is one or two orders of magnitude lower than that of rhodesain.

SECTORS FOR COMMERCIAL APPLICATION

The technology is useful for the pharmaceutical industry, and more specifically for companies dedicated to the development, manufacture and commercialisation of treatments for trypanosomiasis, leishmaniasis, sleeping sickness, Chagas disease or malaria.

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TECHNICAL ADVANTAGES AND COMMERCIAL BENEFITS

The main advantages of the invention are:

- The compounds selectively inhibit parasitic cysteine proteases in humans.
- Simple synthesis: the compounds are synthesised in only two reaction steps using readily-available raw materials and display high performance.

The main innovative aspect of the molecules is their mode of action against the therapeutic target, since they can act as reversible inhibitors or as irreversible inhibitors, which gives them an advantage over other inhibitors. This mode of action contributes to the therapeutic effectiveness of the compound.

STAGE OF DEVELOPEMENT OF THE TECHNOLOGY

The phase involving the synthesis of the compounds has finished. Tests to measure effectiveness have been conducted both in vitro and in cells, all of them yielding positive results. The next step is to perform toxicity testing and start clinical trials.

INTELLECTUAL PROPERTY RIGHTS

Tow European patents have been applied for with the references EP14382283.1 and EP14382307.8, and filing dates 07-17-2014 and 08-04-2014

COLLABORATION SOUGHT

- License agreement for use, manufacturing or commercial exploitation.
- Conducting clinical trials.

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