INHIBITORS OF HSRA FOR TREATING HELICOBACTER PYLORI INFECTION

The present invention describes new bioactive compounds with antimicrobial activity against Helicobacter pylori (H. pylori) by acting specifically on the protein HsrA (essential for cell viability).

Description

Helicobacter pylori is considered the most prevalent human pathogen since nearly half of the world's population is infected by this bacterium. Persistent colonization of human stomach by H. pylori results in gastric inflammation and highly contributes to the pathogenesis of peptic ulceration, gastric adenocarcinoma, and mucosa-associated lymphoid-tissue (MALT) lymphoma. Nearly 60% of the intestinal type gastric cancers and 98% of MALT lymphomas are associated with H. pylori infections. In addition, the presence of H. pylori in the host increases the risk of developing other lymphomas, such as diffuse large B cell lymphoma and ocular adnexal lymphoma.

The standard triple therapy containing a proton-pump inhibitor (PPI) and a combination of two antibiotics (clarithromycin and amoxicillin/metronidazole) is considered the first-line regimen for treatment of H. pylori. However, this PPI-based triple therapy has been reported to be losing its efficacy for H. pylori, with eradication rates as low as 50% to 70%, mainly due to high levels of antibiotic resistance, high rates of antibiotic-associated side effects and low compliance.

The compounds of the invention have high bactericidal activity even on metronidazole and clarithromycin-resistant H. pylori strains through a novel molecular mechanism of antimicrobial action of these compounds on H. pylori: the inhibition of the essential response regulator HsrA.

Innovative aspects

The compounds of the invention are high effective as antibiotics against H. pylori.

These novel antimicrobials are FDA-approved low-molecular-weight drugs prescribed for other therapeutic uses which will considerably reduce the effort required for its implementation.

These compounds are not affected by the molecular mechanisms of metronidazole and clarithromycin resistance evolved by H. pylori.

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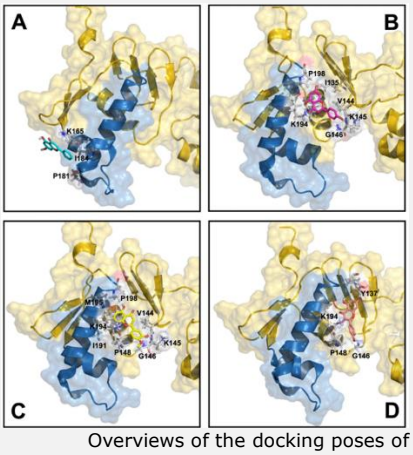

Overviews of the docking poses of compounds of the invention interaction with HsrA. Ribbon model and transparent molecular surface showing the interacting residues of HsrA to each flavonoid. The helix-turn-helix (HTH) DNA binding motif of HsrA is highlighted in blue. Some interacting residues are indicated.

IPR status

Spanish patent application (2018) and international patent application (PCT, 2019) with extension possibilities.

Available for

Further research or development

Exclusive/non-exclusive licence agreement

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