Abstract

Introduction

With the increase in the incidence of gastric cancer in the world and investigation of its causative factors, special attention has been paid to Helicobacter pylori. Helicobacter pylori is the first known carcinogen bacterial and one of the most successful human pathogens, because it is involved the more than half of the world's population. If it is not treated, colonization of this bacterium usually continues. Helicobacter pylori infection is a major cause in variety of gastrointestinal diseases, from asymptomatic chronic gastritis to gastric ulcer. It also plays a major role in the outbreak of gastric cancer or lymphoma malt. Due to the lack of specificity treatment and antibiotic resistance, Helicobacter pylori urease inhibitors can be very effective in preventing and treating high-mortality diseases such as cancer. Therefore, in this project, focusing on urease enzyme and trying to inhibit of this enzyme, 1,2,3,4-tetrahydropyrimidine derivatives were designed and synthesized. Then, the urease enzyme inhibitory power of these compounds was evaluated.

Materials and methods

In the present project, after design of six different 1,2,3,4-tetrahydropyrimidine derivatives, they were synthesized by a one-step Biginelly reaction. Then, their identification and structural confirmation were performed by ^{1}H-NMR, FT-IR and mass spectroscopy. Finally, inhibitory activity of urea enzyme of these compounds was evaluated by Berthelot (phenol-hypochlorite) method.

Results

Summary, the most effective among the synthesized tetrahydropyrimidine derivatives were compounds 6-(4- hydroxyphenyl) -5-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid (N5), with IC_{50} of 6.81 ± 5.4201 µM and 6-(4-hydroxy-3-methoxyphenyl) -5-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid (N6) with IC_{50} of 8.45 ± 3.6417 µM, respectivly and the lowest efficacy was observed in the compound benzyl 4-(4-hydroxyphenyl) -6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (N3) with the IC_{50} of 75.02 ± 2/4145 µM.

Discussion and conclusion

Investigation of the structure-activity relationship shows that the placement of carboxylic acid substitution in the C4 position of tetrahydropyrimidine ring, is due to the ability to form hydrogen or ionic bonds with the active site enzyme and also chelating nickel ion in urease enzyme can significantly increased the inhibitory power of this enzyme. According to results, carboxylic acid group at the tetrahydropyrimidine ring has a positive effect on the inhibitory activity of urease. The presence of the thioxo group in C2 position of tetrahydropyrimidine ring increases the inhibitory activity due to the possibility formation of disulfide bond with the amino acids of the active site.

Keywords: Helicobacter pylori, 1,2,3,4-tetrahydropyrimidine, Biginelly reaction