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Synthesis of 2-Carbamoyl-4-oxo-1,5-diazabicyclo[3.2.1] octane Derivatives as Possible Inhibitors of Serine β-Lactamases

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ABSTRACT

Antibiotic resistance is becoming ever more severe due in part to the increasing use of antibiotic drugs. One significant contributor to this problem is the production of β-lactamase enzymes that provide resistance to common β-lactam antibiotics such as penicillin. The scope of this research is to synthesize and study the β-lactamase inhibitors of 2-carbamoyl-4-oxo-1,5-diazabicyclo[3.2.1] octane derivatives. β-lactamase inhibitors can inhibit the biological function of bacterial β-lactam and aid in the prevention of hydrolysis. Currently the research process is in the beginning stages of synthesizing three compounds: (1) hexahydro-6-oxopyrimidine-4-carboxylic acid, (2) hexahydro-2,2-dimethyl-6-oxopyrimidine-4-carboxylic acid, and (3) hexahydro-6-oxo-2-phenylpyrimidine-4-carboxylic acid. The future steps are to synthesize (R)-3-(methylcarboxyl)-hexahydro-6-oxopyrimidine-4-carboxylic acid, (R)-[dimethyl] tetrahydro-4-oxopyrimidine-1(6H)-carboxylate, and (R)-methyl hexahydro-6-oxopyrimidine-4-carboxylic acid.

INTRODUCTION

Based on molecular structures and amino acid sequences, β-lactamase can be divided into four classes: A, B, C, and D. Class A, C, and D are serine enzymes and are produced at the active site during hydrolysis. In Class B, one or two zinc ions are required at the active site to maintain related biological functions. Class A (e.g. SHV, CTX-M, and SHV) are broad-spectrum β-lactamases and mainly hydrolyze carbapenems such as cephalosporins, aztreonam, and penicillin. The general mechanism is Lys or Glu activation by water followed by nucleophilic attack on carbon in lactam ring by serine. As a result acyl-enzyme intermediate is produced. Clavulanic acid, sulbactam, and tazobactam can form stable covalent complexes and bind to enzyme irreversibly, which results in loss of activity and function of class A lactamases. Clavulanic acid is active against β-lactamases encoded by bla genes on the chromosome.

EXPERIMENTAL PROCEDURE

Compound 1a: To a solution of D-asparaglene(515.52 g) in 400 mL water at 45 °C, add 16.25 mL of 37% formaldehyde. After stirring for 10 hours at 45°C the solution was cooled down to -5°C to give a white slurry. The slurry was allowed to warm up to 0°C, then the precipitate collected by vacuum filtration. The compound then put into oven to dry for over night. Compound 1b: To a mixture of D-asparaglene(2.8 g, 8 mmol) in HPLC grade acetonitrile (12 mL), KOH solid (0.55 g, 9.8 mmol) was added into. The reaction set at oil bath at 120 °C, then do refluxs for 10 hours, magnetic stirring rate set at 400 rpm. Compound 1c: Obtain 1.5 g (10 mmol) D-asparaglene monohydrate, dissolve in 30 mL methanol and input 0.68 g (20 mmol) potassium hydroxide, then add 1.34 mL benzylaldehyde dropwise, and the reaction mixture was kept at 25 °C for 12 hours. Then add 10 mL ether to the reaction flask to wash and filtrate to obtain white solid.

INHIBITOR DESIGN

Retrosynthetic analysis:

Scheme 1. Synthetic route of compound(1a), hexahydro-6-oxopyrimidine-4-carboxylic acid, compound(1b), hexahydro-2,2-dimethyl-6-oxopyrimidine-4-carboxylic acid and compound(1c), hexahydro-6-oxo-2-phenylpyrimidine-4-carboxylic acid.

RESULTS

CONCLUSION

We have synthesized several compounds (1a-c) and we are currently in the process of producing 3a derivatives (2a, 3a, and 4a). All chemical structures were characterized based on 1H- and 13C-NMR spectra. We will continue our multiphisty synthesis pathway to make the target compound. The biological activity of all compounds will be tested in collaboration with other research groups. The focus of our bioassay will be on antibacterial potency and/or inhibitory activity against class A and C serine β-lactamases.

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