Design and Synthesis of Potential Aminoacyl-tRNA Synthetase Inhibitors

ITEDALE NAMRO REDWAN

GÖTEBORGS UNIVERSITET

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Akademisk avhandling för filosofie doktorsexamen i Kemi med inriktning mot läkemedelskemi som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredagen den 11 maj 2012 kl. 09.00 i sal KC, Institutionen för kemi, Kemigården 4, Göteborg.

Fakultetsopponent är Ramón Eritja, Institute for Research in Biomedicine, Barcelona, Spain.

Abstract

Aminoacyl-tRNA synthetases (aaRSs) are essential enzymes present in all living organisms, their catalytic activity is involved in the translation of the genetic code into functional proteins and they are potential targets for anti-infective agents. The first step in the biosynthetic pathway catalysed by aaRSs consists of activation of the corresponding amino acid by the reaction with ATP to form an aminoacyl-adenylate (aa-AMP), the key intermediate in the biosynthesis of proteins. As a result stable, analogues of aa-AMP have been identified as potential and valuable lead compounds for the development of potential aaRS inhibitors.

This thesis describes the design and synthesis of potential aaRSs inhibitors. The studies involve the development of a novel solution-phase synthetic route to non-hydrolysable sulfamoyl-based aa-AMP analogues. Synthesis includes the development of a protective group strategy that utilises global deprotection under neutral conditions to minimise by-product formation. Optimal reaction conditions for the coupling of different amino acids to the sulfamoyl moiety have also been investigated.

A solid-phase synthetic route leading to non-hydrolysable sulfamoyl-based aa-AMP analogues has also been developed. The novel synthetic route enables the possibility for rapid parallel synthesis of structurally diverse compounds in quantities sufficient for biological evaluation.

Molecular modelling techniques have been used to gain understanding about the structure–activity relationship of the inhibitors of aaRSs based on non-hydrolysable aa-AMP analogues. A model ligand adopting the putative bioactive conformation was identified based on X-ray data and conformational searches. Novel phosphate bioisosteres of aa-AMP have been designed using the derived model.

Molecular docking techniques were used for the design of ribose-free purine-based aa-AMP bioisosteres. The designed compounds were synthesised and evaluated biologically in an assay using aaRS isolated from *Escherichia coli.*

A novel mild method for the activation and recycling of a tritylated solid-phase resin has also been developed. Recycling of recovered resin after the completion of a reaction is considered beneficial since it minimises the associated costs and is environmentally friendly. The method was used for the attachment of primary and secondary alcohols, halogen-containing alcohols and anilines to trityl resin.

Keywords: Aminoacyl-tRNA synthetases, Aminoacyl-AMP, Bioisosteres, Amino Acids, Solution-Phase Chemistry, Protective Groups, Solid-Phase Chemistry, Biological Evaluation

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