Accepted Manuscript

New isoxazolidinone and 3,4-dehydro-β-proline derivatives as antibacterial agents and MAO-inhibitors: A complex balance between two activities

Lucia Ferrazzano, Angelo Viola, Elena Lonati, Alessandra Bulbarelli, Rosario Musumeci, Clementina Cocuzza, Marco Lombardo, Alessandra Tolomelli

PII: S0223-5234(16)30735-8

DOI: 10.1016/j.ejmech.2016.09.007

Reference: EJMECH 8873

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 26 July 2016

Revised Date: 1 September 2016

Accepted Date: 2 September 2016

Please cite this article as: L. Ferrazzano, A. Viola, E. Lonati, A. Bulbarelli, R. Musumeci, C. Cocuzza, M. Lombardo, A. Tolomelli, New isoxazolidinone and 3,4-dehydro-β-proline derivatives as antibacterial agents and MAO-inhibitors: A complex balance between two activities, *European Journal of Medicinal Chemistry* (2016), doi: 10.1016/j.ejmech.2016.09.007.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Journal

New isoxazolidinone and 3,4-dehydro-β-proline derivatives as antibacterial agents and MAO-inhibitors: a complex balance between two activities.

Lucia Ferrazzano[a], Angelo Viola[a], Elena Lonati[b], Alessandra Bulbarelli[b], Rosario Musumeci[b], Clementina Cocuzza[b], Marco Lombardo[a], Alessandra Tolomelli[a]*.

[a]*Department of Chemistry, University of Bologna, Via Selmi 2, 40126, Bologna, Italy*
[b]*Department of Medicine and Surgery, University of Milano-Bicocca, Via Cadore 48, 20900, Monza, Italy*

ABSTRACT

Among the different classes of antibiotics, oxazolidinone derivatives represent important drugs, since their unique mechanism of action overcomes commonly diffused multidrug-resistant bacteria. Anyway, the structural similarity of these molecules to monoamino oxidase (MAO) inhibitors, like toloxatone and blefoxatone, induces in many cases loss of selectivity as a major concern. A small library of compounds based on isoxazolinone and dehydro-β-proline scaffold was designed with the aim to obtain antibacterial agents, evaluating at the same time the potential effects of structural features on MAO inhibitory behaviour. The structural modification introduced in the backbone, starting from Linezolid model, lead to a significant loss in antibiotic activity, while a promising inhibitory effect could be observed on monoamino oxidases. These interesting results are also in agreement with docking experiments suggesting a good binding pose of the synthesized compounds into the pocket of the oxidase enzymes, in particular of MAO-B.

1. Introduction

The increase of phenomena of antibiotic resistance became a central matter in public health programs, since it represents a problem not only for people already infected, but also for the diffusion of resistant bacteria to other people.[1] The problem grew with the appearance of multidrug-resistant ESKAPE pathogens (*Enterococcus* spp, *Staphylococcus aureus, Klebsiella* spp, *Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp), usually causes of chronic infections like skin infections, meningitis, urogenital tract diseases and respiratory tract infections. This emergency justifies the continuous research for new type of antibiotics. Between the most recent classes of antibiotics, oxazolidinones represent a great innovation in the attempt of limiting the diffusion of "smartly" modified Gram-positive bacteria. Linezolid (Zyvox®) represents a well-known antimicrobial agent able to fight Vancomicyn-Resistant Enterococci (VRE), Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Penicillin-Resistant *Streptococcus pneumoniae* (PNSSP).[2-3] Like other molecules belonging to the family of oxazolidinones, Linezolid's mechanism of action regards the binding to peptidyltransferase centre (PTC), corresponding to 50S subunit of prokaryotic ribosome. The structure of Linezolid consists in four chemical moieties that can justify its interaction with the ribosomal binding site (Figure 1). Ring-A is the pharmacokinetic oxazolidinone ring and interacts with fixed residues of the PTC pocket through van der Waals interactions. The acetamide NH on the tail participates in hydrogen bond with the phosphate group on a residue in the upper part of the pocket. The oxazolidinone fits, together with the C5-tail, in the direction of the ribosomal tunnel, orienting the ring-C toward the inter-subunit interface. Ring-B is sandwiched through π-staking with two residues and participates in a T-shaped interaction, while the C2 fluorine points out of the pocket to contribute to the coordination of a putative magnesium ion that appears upon Linezolid binding in this particular configuration. The morpholine in Ring-C, does not give particular interactions with the binding site but has great importance in the modulation of molecule pharmacokinetic.[4-5] Despite all these favourable features, there are several cases of resistance to Linezolid.[6]

Considering their efficacy and evaluating the chance to introduce modifications to reduce resistance effects, oxazolidinones were deeply studied in their structure-activity relationships (SAR) in order to identify bioisosters of each part of the molecule, in particular of Ring-A. These studies revealed that bioisosteric modifications on Ring-A should maintain i) an sp^2 centre directly linked to Ring-B, ii) an oxygen atom properly located and iii) a C5-chiral centre stereochemically defined carrying the acylaminomethyl chain.[7] These requirements were confirmed by the results in terms of inhibition of the

Download English Version:

https://daneshyari.com/en/article/7797759

Download Persian Version:

https://daneshyari.com/article/7797759

Daneshyari.com