Ashley Publications

Expert Opinion on Therapeutic Patents

Vol. 9 No. 5

May 1999

Expert Opinion on Therapeutic Patents

http://www.ashley-pub.com

Commissioning Editor: Liz Williams
Production Editor: Paula Rhodes
Publisher: James Drake

Aims and scope: *Expert Opinion on Therapeutic Patents* aims to provide an evaluated guide to developments in the recent patent literature. The journal is divided into six therapeutic sections. Each section is reviewed every six months, allowing systematic and comprehensive coverage of the most important topics:

- Pulmonary-Allergy, Dermatological, Gastrointestinal & Arthritis (January & July)
- Anti-infectives (February & August)
- Biologicals, Immunologicals & Drug Delivery (March & September)
- Central & Peripheral Nervous Systems (April & October)
- Cardiovascular & Renal (May & November)
- Oncologic, Endocrine & Metabolic (June & December)

Authors are encouraged to express their *Expert Opinion* of the status of the research under review, rather than to simply review the available data. Each issue of the journal contains annotated patent selections and short patent evaluations which highlight inventions and innovative ideas deemed by relevant experts to be of potential importance.

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Annual subscription rates: *Expert Opinion on Therapeutic Patents*, Volume 9, 12 monthly issues, £1750 / US$3235 / ¥494,950.

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Review

Recent developments with oxazolidinone antibiotics

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The emerging problems with multiple antibiotic-resistant Gram-positive cocci led to the re-evaluation of an antibacterial class of compounds, the oxazolidinones. During the 1990s, many companies such as Upjohn, Bayer, Zeneca, Roussel Uclaf, Marion Merrell Dow and Glaxo published their work on antibacterial active oxazolidinones. The primary work in this area started in the 1980s at DuPont. The efforts of these scientists led to N-phenyl and N-heteroaryl oxazolidinones with strong antibacterial activity *in vitro* and *in vivo*. The most advanced oxazolidinone, linezolid, discovered by scientists at Upjohn, is currently undergoing Phase III clinical trials.

Keywords: *antibiotic, DuP-721, enterococci, eperezolid, Gram-positive, linezolid, methicillin-resistant Staphylococcus aureus, methicillin-resistant Streptococcus epidermidis, monoamine oxidase inhibitors, mycobacteria, N-phenyl oxazolidinone, N-pyridyl oxazolidinone, N-thienyl oxazolidinone, oxazolidinone, penicillin-resistant Streptococcus pneumoniae, staphylococci, vancomycin-resistant enterococci*

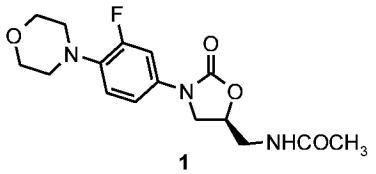
*Exp. Opin. Ther. Patents (1999) **9**(5):625-633*

1. Introduction

The evolution and spread of resistance to currently available antimicrobial agents in important pathogens is a serious medical problem [1-3]. In particular, infections caused by multiresistant Gram-positive cocci are a threat in antibacterial therapy. Therefore, the primary focus of the worldwide antibiotic discovery programs is the identification of new compound classes with novel mechanisms of action.

The oxazolidinones represent a relatively new class of orally active, synthetic antimicrobial agents with a Gram-positive spectrum of activity. They inhibit an early event in the bacterial protein biosynthesis [4-6]. After sequencing the ribosomal RNA genes of oxazolidinone-resistant strains and comparing it to sensitive parental strains, mutations were found in the peptidyl transferase domain of the 23S rRNA [7]. This supports earlier results that demonstrated oxazolidinone binding to the 50S subunit of the ribosome [8-10]. A recent publication [11] describes the target for oxazolidinones in more detail. Drug binding sites were found on both ribosomal subunits. The 16S and the 23S rRNAs are directly involved in oxazolidinone binding. Furthermore, the inhibition of tRNA translocation is discussed as mechanism of action.

Oxazolidinones with antibacterial activity such as 5-*(S)*-acetamidomethyl-3- aryl-2-oxazolidinones were first described in the 1980s by scientists from DuPont [12-14]. In 1987 at the 27th ICAAC, DuPont presented two candidate compounds DuP-721 [15-17] and DuP-105 [15,16],



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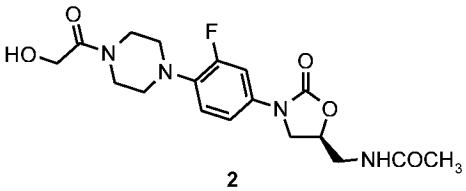

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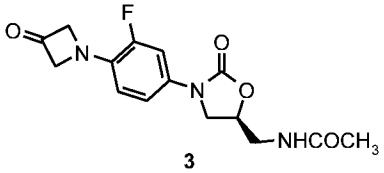

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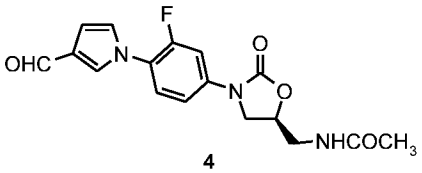

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demonstrating high *in vitro* and *in vivo* activity *vs.* Gram-positive pathogens and *Mycobacterium tuberculosis* [18].

The increasing clinical problems with multiresistant pathogens along with the attractive properties of the oxazolidinones encouraged workers at Upjohn to start a discovery program [19]. These efforts led to two clinical candidates, eperezolid (**2**, U-100592) and linezolid (**1**, U-100766) [20,21]. Both compounds exhibited potent *in vitro* activity against Gram-positive bacteria, including multiresistant strains [22,23]. In various experimental infections, these oxazolidinones demonstrated excellent therapeutic efficacy [24]. Toxicological studies of the candidates in rats and dogs showed a favourable safety profile. In Phase I studies using either p.o. or iv. dosing, eperezolid (**2**) and linezolid (**1**) achieved plasma concentrations above the MIC values of relevant pathogens [25]. Both oxazolidinones are well-tolerated in humans at clinically relevant doses [26]. For a given dose, linezolid (**1**) produced higher plasma levels than eperezolid (**2**). Due to its advantageous pharmacokinetic profile, Upjohn continued the clinical development program with linezolid (**1**). During Phase II clinical trials, linezolid (**1**) was studied in a dose range of 750 - 1000 mg/day for up to 21 days. The oxazolidinone showed good efficacy and excellent tolerability. Phase III clinical trials are underway.

Bayer has also taken interest in this compound class and new N-heteroaryl oxazolidinones with improved antimicrobial activity have been prepared. Modifications of the oxazolidinone core unit have been reported by Zeneca, Marion Merrell Dow [27], Roussel Uclaf [28], Glaxo [29] and Pharmacia & Upjohn.

In addition to the antimicrobial activity, other pharmacological activities of the oxazolidinones have been reported.

A comprehensive review from Brickner [19] discussed the structure-activity relationship (SAR) findings of DuPont and Upjohn and described in detail the oxazolidinones that entered clinical trials. Our review will focus on the recent activity selected from the patent literature since 1996.

2. N-Phenyl oxazolidinones

The N-phenyl oxazolidinones are the most advanced series of antibacterial oxazolidinones, first described by DuPont in the 1980s.

DuPont presented compounds bearing a *(S)*-5-acetamidomethyl side-chain, DuP-721 and DuP-105. Both oxazolidinones demonstrated good *in vitro* and *in vivo* activity against Gram-positive pathogens. These parentally and orally active candidates entered Phase I clinical trials, but the development was later discontinued for tolerability reasons.

Scientists at Upjohn focused on fluorine substituted N-phenyl oxazolidinones [30].

The most promising representative of the 3-fluoro-N-phenyl-oxazolidinone series is linezolid (*(S)*-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo--5-oxazolidin-yl]methyl]-acetamide) (**1**) [116], which was identified in the early 1990s. It possesses good *in vitro* and *in vivo* potency *vs.* Gram-positive bacteria such as staphylococci [31], pneumococci [32] and enterococci [33,34], including resistant strains (methicillin-resistant *Staphylococcus aureus* [MRSA], methicillin-resistant *Streptococcus epidermidis* [MRSE], penicillin-resistant *Streptococcuspneumoniae* [PRSP], vancomycin-resistant enterococci [VRE]). Linezolid (**1**) is currently in clinical development

(Phase III) for severe hospital infections. The 3-fluoro-N-phenyl subclass seems to have both good *in vivo* potency and low toxicity.

Antibacterial therapy of intensive care unit (ICU) patients requires iv.-treatment. Most of the antibacterial oxazolidinones are insoluble in water and are therefore causing difficulties in finding a suitable iv. formulation. Upjohn described the water solubility and antibacterial activity of N-oxides [117] including the N-oxide of linezolid (**1**). This N-oxide retained most of linezolid's antibacterial activity (MIC = 4 µg/ml *vs. S. aureus* UC 9213) and had good water solubility (N-oxide 348 mg/ml, linezolid 3.7 mg/ml). This prodrug approach should help in finding suitable iv. formulations for oxazolidinones. This is not necessary for linezolid (**1**) since there is an appropriate iv. formulation already in use.

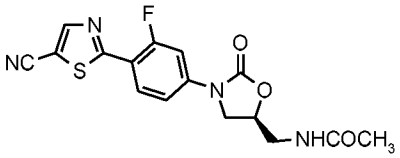
The main focus of the discovery program at Upjohn was the evaluation of the SAR around the 3-fluoro-N-phenyl oxazolidinones. The common feature of these 3-fluoro-N-phenyl oxazolidinones is a nitrogen containing heterocycle attached to the 4-position of the phenyl ring.

Small four- and five-membered heterocycles were described in 1996 [101], and exhibited reasonable *in vitro* potency (**3**, MIC *vs. S. aureus* or *Streptococcus pneumonia* ~ 1 - 4 µg/ml).

N-Fluorophenyl oxazolidinones substituted with bicyclic nitrogen containing heterocycles were described [102,107] and exhibited good efficacy after oral dosing (ED_{50} ~ 5 mg/kg) in murine infections caused by *S. aureus*.

Aromatic five-membered nitrogen containing heterocycles in the 4-position of the N-phenyl oxazolidinones increased the *in vitro* potency 2- to 4-fold compared to the corresponding non-aromatic analogues. These compounds were described by scientists from Upjohn [103] and Zeneca [104]. Formyl groups as substituents in the distal ring (**4**) increased the activity. The same effect was observed by Bayer scientists [105] in the N-heteroaryl oxazolidinone series. These formyl compounds cannot translate their excellent *in vitro* potency into *in vivo* efficacy (due to pharmacokinetic and metabolic problems).

The most promising compounds in the N-(3-fluorophenyl)oxazolidinone series, substituted with a five-membered aromatic heterocycle, are the thiazole substituted compounds [35]. *(S)*-N-(3-(3-Fluoro-4-(2-(5-cyanothiazolyl))phenyl-2-oxo-5-oxazolidinyl)methyl)acetamide (**5**) exhibited very strong antibacterial *in vitro* activity against Gram-positive cocci (MIC *vs. S. aureus* <0.125 µg/ml) as well as against fastidious Gram-negative organisms (MIC *vs. Haemophilus influenzae* 30063 ~ 2 µg/ml).



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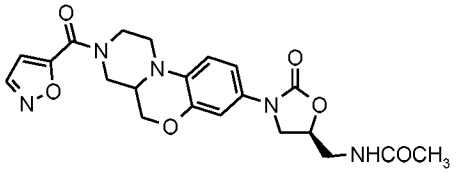

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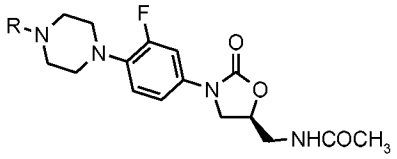

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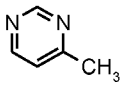

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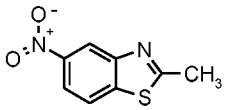

The left side of the molecule allows for many variations. Besides the above mentioned small four- and five-membered heterocycles, large tricyclic systems connected to the oxazolidinone still showed reasonable *in vitro* potency [106] (**6**, MIC *vs. S. aureus* ~ 2 - 4 µg/ml).

Another field of intense research within the area of N-phenyl-oxazolidinones are the piperazine derivatives exemplified by *(S)*-N-(3-(3-fluoro-4-(4-(4-pyrimidinyl)-1-piperazinyl)phenyl-2-oxo-5-oxazolidinyl)methyl)acetamide (**7**). Scientists from Upjohn [108] and Zeneca [109,110] reported compounds with good MIC values and reasonable *in vivo* potency (**7**, ED_{50} = 4.4 mg/kg, *S. aureus* infection in mice). The heterocycles in 4-position of the piperazine unit are mainly pyrimidine, pyridine and other nitrogen containing five- and six-membered heterocycles [36]. Even large substituents like 2-(6-nitrobenzothiazole) on the piperazine unit [111] exhibited strong potency *vs.* Gram-positive bacteria (**8**, MIC *vs.*

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