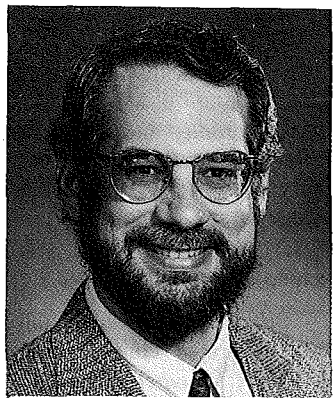
Oxazolidinone Antibacterial Agents



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Abstract: The oxazolidinones are a new class of synthetic antibacterial agents. These compounds demonstrate potent *in vitro* and *in vivo* activity against important human pathogens, including multiple antibiotic-resistant strains of gram positive organisms including the staphylococci, streptococci, and enterococci. The oxazolidinones have a novel mechanism of action, inhibiting bacterial protein synthesis at a very early step prior to initiation. Literature disclosures have described the inability to detect *in vitro* bacterial resistance development to the oxazolidinones. Only the (S)-enantiomer is active; a new synthetic route yielding oxazolidinones with high optical purity has been reported. This paper will review the spectrum of activity, mechanism of action studies, toxicity issues, and structure activity relationships of the oxazolidinones.

Introduction

The oxazolidinones are novel synthetic antibacterial agents that show considerable promise for the treatment of human infections caused by problematic multi-drug resistant and sensitive gram-positive bacteria and *Mycobacterium tuberculosis* [1]. If the drugs currently in development are proven efficacious in man, the oxazolidinones would represent the first new class of antibacterial agents to be developed in over a decade.

Following an account of the discovery and early lead development by DuPont that led to the 5-acetamidomethyl-3-aryl-2-oxazolidinones, the major focus of this review turns to an extensive survey of the more relevant structure-activity relationship [SAR] findings. In-depth discussion also centers on those few oxazolidinones that have entered the drug development process, and have proceeded at least as far as Phase I human clinical trials.

Given that this is a burgeoning area of research, the relatively few publications in the open literature have been supplemented with selected biological data gleaned from published patents, patent applications, and meeting abstracts. Various associated compounds that are best classified as members of other antimicrobial drug classes, yet happen to contain an oxazolidinone ring substituent,[0] are excluded from the realm of this review. Discussion will also be found concerning aspects of the monoamine oxidase [MAO] inhibitory properties of certain 5-(substituted)methyl-3-aryl-2-oxazolidinones[1] (eg., 5-hydroxymethyl [5] or 5-aminomethyl groups [6]), as such compounds have considerable synthetic utility as chemical intermediates to the subject compounds, or may themselves exhibit some degree of antibacterial activity.

Nomenclature

The antibacterial oxazolidinone pharmacophoric template can be characterized as that depicted in Fig. (**1**), i.e., an (S)-3-aryl-5-(substituted)methyl-2-oxazolidinone. Throughout the review, a consistent numbering system has been employed for description of the various oxazolidinones examined.[2]

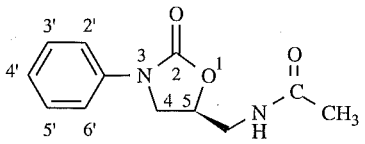

Fig. (1). Oxazolidinone numbering scheme.

Bacterial Resistance and the Search for Novel Antibiotic Structural Templates

The alarming escalation seen worldwide in the incidence of bacterial resistance to previously effective antibiotics [7], continues to provide the impetus for the medicinal chemist to search for entirely new classes of antibacterial agents, that can cure bacterial infection by novel mechanisms [8,9]. As numerous bacteria have increasingly evidenced the evolution of multiple-antibiotic resistance, health care providers have been seriously challenged to provide effective therapy for the often life-threatening infections caused by these pathogens. Numerous reviews have recently appeared emphasizing the extent and severity of the resistance problem as it exists today, and the dim prospects envisioned for the future [10-14].

Some of the most problematic organisms of the 1990's have been the multi-drug resistant gram-positive bacteria. These include the highly virulent organism, methicillin-resistant *Staphylococcus aureus* [MRSA] [9], and penicillin- [15] and cephalosporin-resistant *Streptococcus pneumoniae*. For many strains of MRSA, only vancomycin is still effective [10], as such MRSA isolates are also found resistant to virtually all penicillins and cephalosporins, tetracyclines, aminoglycosides, lincosamides, chloramphenicol, macrolides [16], and quinolones [17-19].

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[0]These include the nitrofuran furazolidone [2] and the 3-chloro oxazolidinone bactericides [3].

[1]Oxazolidinones having MAO inhibitory properties have been known for

[2]Designation of regiochemistry of substitution about the 3-aryl ring is indicated by the use of primed (') numerals. Where an additional aryl ring is linearly appended, double-primed (") numbering is employed for that ring. For the sake of clarity the same system has been applied to describe more structurally complex, multicyclic fused ring templates, in lieu of the

The enterococci have become increasingly of concern, in that over the last five years, there have been isolated problems of infections with vancomycin-resistant enterococci [VRE] [11]. The VRE are also resistant to essentially all other antibiotics [20]. Mortality rates greater than 35% have been reported for patients infected with VRE [21]. A major concern is that VRE will transfer the vancomycin-resistance genes encoded on a plasmid [22], to the much more virulent organism *S. aureus*, as Noble et al. [9] have demonstrated to be feasible in an experimental setting.

Still another problem microorganism for which resistance has generated considerable medical concern is multidrug-resistant *M. tuberculosis* [MDRTB] [23]. *M. tuberculosis* is a highly virulent human pathogen that is the cause of approximately 3 million deaths per year worldwide [24]; strains resistant to isoniazid [INH] are widespread throughout the world. Infections with *M. tuberculosis* are now commonly treated in the USA with a combination of INH, rifampin, and pyrazinamide [25].

This loss of antibacterial activity among drugs once efficacious against these pathogens, has led to a summoning from numerous experts [14,26] for the discovery and development of new antibiotic classes, so that health care practitioners will not be left bereft of effective therapeutic modalities [27]. The oxazolidinone antibacterial agents may, if demonstrated to be efficacious in man, provide an answer to this call as the first new class of antibiotics to be developed since the fluoroquinolones [19].

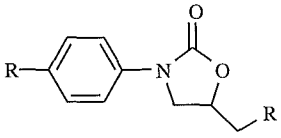
Discovery of the Oxazolidinone Antimicrobial Agents

5-Halomethyl-3-Aryl-2-Oxazolidinones

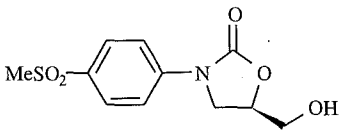
In a 1978 U.S. patent assigned to E.I. du Pont de Nemours and Co., Inc., Fugitt and Luckenbaugh [28] described a series of racemic 5-halomethyl-3-aryl-2-oxazolidinones[3] which were claimed to have utility for the systemic control of bacterial and fungal foliage diseases of plants. Synthesis of the oxazolidinone ring was accomplished by heating an isocyanate and an epihalohydrin with a lithium halide catalyst.

Application to tomato plants of a 200 ppm suspension of 5-(chloromethyl)-3-(4'-methylthio)phenyl-2-oxazolidinone **1**, or its corresponding 4'-methylsulfonyl congener **2**, prior to inoculation with either *Agrobacterium tumefaciens* or *Xanthomonos vesticatoria*, was effective in preventing the establishment of disease manifested as crown gall or leaf spot.[4]

Subsequently, a patent issued to the same inventors [32] which described the antibacterial activity of related 5-halomethyl-2-oxazolidinones against bacterial pathogens infective of mammals. 5-Chloromethyl oxazolidinones **2** and **3**, and 5-bromomethyl oxazolidinone **4** demonstrated good *in vitro* activity against *Staphylococcus epidermidis*, with minimum inhibitory concentrations [MICs] of 5, 2.5, and 5 μg/mL, respectively. In lethal infection models in mice, oral administration [po] of **2** or **3** required a dose to protect 50% of the infected animals [ED_{50}] of 29 mg/kg and 20 mg/kg *vs S. aureus*, respectively. Weak activity (ED_{50}=63 mg/kg) was observed for **2** *vs* the gram-negative *Escherichia coli*.



1 X = Cl R = MeS
2 X = Cl R = $MeSO_2$
3 X = Cl R = F_2HCSO_2
4 X = Br R = $MeSO_2$



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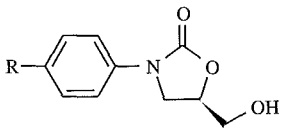
5-Hydroxymethyl-3-Aryl-2-Oxazolidinones

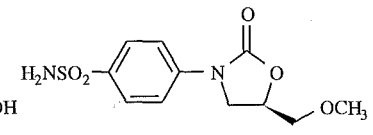
The same patent [32] also described antibacterial 5-hydroxymethyl-3-aryl-2-oxazolidinones and the corresponding esterified alcohols. Most active *in vivo* was the optically active 5-(*R*)-hydroxymethyl-3-(4'-methylsulfonyl)phenyl-2-oxazolidinone **5**, prepared *via* diethylcarbonate-mediated cyclization of *d*-3-(4-methylthioanilino)-1,2-propanediol, then oxidation with MCPBA. The resultant sulfone **5** exhibited reasonable *in vitro* and *in vivo* activity *vs S. aureus* (Table **I**).

S-6123 and (*R*)-5-(Methoxymethyl)-3-[4'-(Methylsulfonyl)Phenyl]-2-Oxazolidinone

In 1984, Gregory [33] disclosed a series of 5-hydroxymethyl-, 5-acetoxymethyl-, and 5-methoxymethyl-3-aryl-2-oxazolidinone antibacterial agents, wherein the preferred compounds bore 4'-(H_2NSO_2)- or 4'-$MeSO_2$- aryl substituents. **S-6123**, and the 5-methoxymethyl analog **6** had notable potency (Table **I**). While **S-6123** was singled out for further study, relative to the subsequently developed *5-acetamidomethyl*-2-oxazolidinone congeners, it exhibited only weak *in vitro* antibacterial activity [34,35]. Nevertheless, Daly et al. [34] reported that upon po administration of **S-6123** (at a level producing a serum concentration of only one-tenth the MIC), 20 of 23 rats survived a lethal *E. coli* peritonitis challenge. On an ED_{50} basis, compound **6** had better *in vivo* activity than **S-6123** (Table I) [33]. For the sake of comparison with the corresponding 5-acetamidomethyl-2-oxazolidinone clinical candidate **DuP 721** (*vide infra*), Table **I** also gives *in vivo* data for the much less active (±)-3-(4'-acetyl)phenyl-5-hydroxymethyl-2-oxazolidinone (**7**) [33]. Any further developmental activity with either **6** or **S-6123** was not evidenced in the literature.



S-6123 R = H_2NSO_2
7 R = MeCO



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[3]The author presumes that these are the lead compounds reportedly [29,30] discovered as a result of random screening.

[4]A Bayer A. G. group [31] recently filed a patent application describing

Table I. Antibacterial Activity of 5-Hydroxymethyl Oxazolidinones

Organism	Mean MIC(μg/mL)[1] 5[33]	S-6123[33,34]
Streptococci spp.	3.7	8-32
Staphylococci spp.	3.8	22-64
E. coli	21.7	30
Salmonella spp.	16	32
Neisseria spp.	10.5	12
Haemophilus influenzae	16	32
Clostridium spp.	7	17
Bacteroides spp.	3.4	≥15
Fusobacterium spp.	0.3	1

	ED_{50}(mg/kg) 5	S-6123	6	7
S. aureus	9	17.1	5.1	35.8
E. coli	25	13.2	11.8	97.6

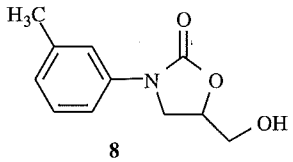
[1]Mean MIC for multiple isolates

MAO Inhibition

In view of the pharmacological activity of a class of reversible and competitive MAO inhibitors [36] having the 5-hydroxymethyl-3-aryl-2-oxazolidinone pharmacophore (eg., antidepressant toloxatone **8** [37]), or the 5-methoxymethyl-3-aryl-2-oxazolidinone template (eg., cimoxatone **9** [38]), there is some concern whether the antibacterial 3-aryl-2-oxazolidinones bearing these side-chains could potentially engender undesirable side-effects, *via* inhibition of mammalian MAO-A or MAO-B isozymes [6,37,39].

More pertinent with respect to the antibacterial 5-acetamidomethyl-3-aryl-2-oxazolidinones (*vide infra*), are the 5-aminomethyl-3-aryl-2-oxazolidinones that are known to inhibit MAO [78]. Compound **10** [79] was reported to be a reversible inhibitor of MAO-B. Interestingly, Silverman and Ding [79] showed that synthetic conversion of this primary amine to the corresponding secondary amine (5-methylaminomethyl) or tertiary amine [5-(N,N-dimethylaminomethyl)] side-chains transformed the oxazolidinones into irreversible inactivators of MAO. The irreversible [76] MAO-B inhibitor **MD780236** [5,39] is one of the most potent oxazolidinones, being selective for MAO-B.[5] Dostert and coworkers [80] have also shown that **10**, the *S*-enantiomer of the primary amine derivative corresponding to **MD780236**, is a potent inhibitor of semicarbazide-sensitive amine oxidase. Thus, there may be potential side-effect implications should the antibacterial 5-acetamidomethyl-2-oxazolidinone (*vide infra*) undergo metabolic amide cleavage, to generate a 5-aminomethyl-2-oxazolidinone.

Silverman [76,81] and Strolin-Benedetti [38] have extensively studied the mechanism of inactivation of the flavoenzyme MAO by these and related oxazolidinones. In the case of the 5-(methylamino)methyl oxazolidinones, one mechanism for the inactivation of MAO-B was proposed to involve one-electron oxidation of the methylamine [81]. Loss of a proton from the amine radical cation resulted in a radical that can covalently link with an amino acid residue in the enzyme, resulting in enzyme-inactivation [76]. An alternative mechanism involves the oxidation of the amine to an imine (or aldehyde [39]), which then traps a nucleophilic amino acid residue [76]. For a discussion of the proposed binding mechanism of the 5-hydroxymethyl-3-aryl-2-oxazolidinones, refer to Koenig [37].



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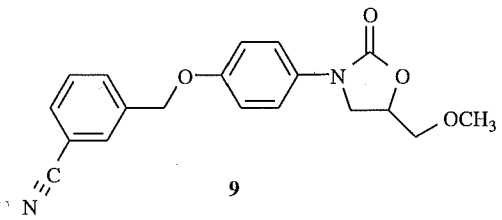

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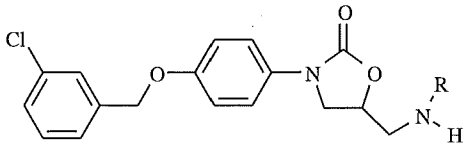


MD 780236 R = Me
10 5-(S) R = H

5-(*S*)-Acetamidomethyl Oxazolidinones

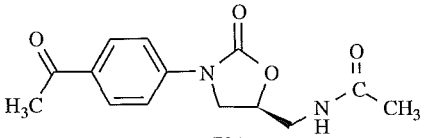
DuPont Clinical Candidates DuP 721 and DuP 105

The first description of 5-(*S*)-acetamidomethyl-3-aryl-2-oxazolidinone antibacterial agents is found in a 1984 patent application [1]. In late 1987, the DuPont group [40,83] presented detailed information on two oxazolidinones bearing the (*S*)-5-acetamidomethyl side chain: **DuP 721**[6], and **DuP 105**[7]. These parenterally and orally active oxazolidinones were identified as members of a new class of synthetic antibacterial agents, having a novel mechanism of action [40,41]. Only the *5-S* enantiomer of the oxazolidinones is active [29].

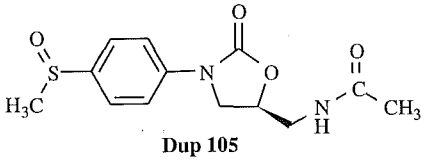
Unlike **S-6123**, **DuP 721** demonstrated potent *in vitro* and *in vivo* activities against gram-positive pathogens, including MRSA, *Staphylococcus epidermidis*, *S. pneumoniae*, and enterococci, as well as against anaerobes, and *M. tuberculosis* [42] (Table **II**). There was no inhibitory activity against gram-negative aerobes, or *Candida albicans* [30,43]. In a lethal mouse

[6](*S*)-N-[[3-(4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide

model, **DuP 721** demonstrated activity (ED_{50}=2.2 and 2.8 mg/kg, sq and po, respectively) better than, or comparable to, vancomycin (sq) for MRSA. Against *E. faecalis* and methicillin-sensitive *S. aureus*, **Dup 721** had ED_{50} values of 2.5-3.1 mg/kg and 3.9-5.6 mg/kg, respectively, being considerably more potent than vancomycin.



Dup 721



Dup 105

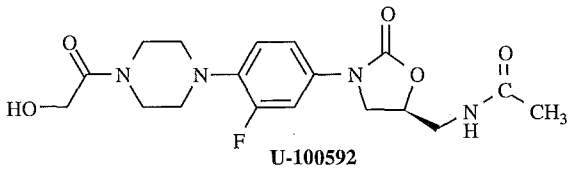
In a number of studies, the *in vitro* potency of **DuP 721** was found to be somewhat less than vancomycin for most gram-positive organisms, with MIC_{90} values of 4 μg/mL for *S. aureus* (methicillin-sensitive or resistant) [30,44], and 1-4 μg/mL for the streptococci and enterococci [30]. The MIC_{90} for *Bacteroides fragilis* was 4 μg/mL. **DuP 105** was approximately 4-fold less active than **DuP 721**, and several fold less active *in vivo* than vancomycin for most organisms [30,41, 45-50]. The antibacterial spectrum of both **DuP 721** and **DuP 105** was represented as most closely resembling that of lincomycin [43]. Both compounds were bacteriostatic [30]. Several studies demonstrated the inability to select for resistant variants to **DuP 721** or **DuP 105** [41,43,45].

A two-fold difference in activity for the two **DuP 105** diastereomers was noted, with the *R*-absolute configuration of the methylsulfinyl group being most active [51]. This *R,S* diastereomer was extremely water soluble (782 mg/mL), in contrast to the S,S diastereomer (112 mg/mL). The mixture of diastereomers (i.e., **DuP 105**), had a solubility of 311 mg/mL.

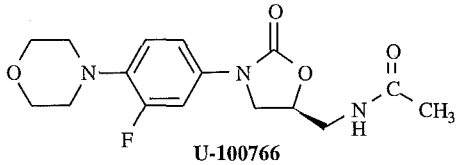
DuP 721 [52] and **DuP 105** [53] reportedly entered Phase I clinical trials, but the development of each was subsequently discontinued [54,55]. It should be noted that Piper and coworkers at Upjohn[8] found **(±)-DuP 721** to exhibit lethal toxicity in the rat (*vide infra*).

Upjohn Clinical Candidates U-100592 and U-100766

In late 1995, a team from the Upjohn Co. [56-62] reported on the development of two (*S*)-5-acetamidomethyl-2-oxazolidinones that were in late Phase I clinical trials and slated to enter Phase II studies. **U-100592**[9] and **U-100766**[10] were 3-(3'-fluorophenyl)-2-oxazolidinones that, like **DuP 721,** exhibited *in vitro* and *in vivo* antibacterial activity comparable to vancomycin (Table **II**), but did not have the toxicity observed with **(±)-DuP 721**[8] [63].



U-100592



U-100766

U-100592 and **U-100766** were under development for the treatment of gram-positive infections caused by both sensitive and drug-resistant strains of staphylococci, streptococci, and enterococci. Formulations were available allowing both drugs to be administered by iv and oral routes. Zurenko et al. [57] showed that neither drug was cross-resistant with vancomycin for enterococci, nor with penicillin for pneumococci. Activity comparable to tetracycline was observed against the *Mycoplasma* spp., respiratory pathogens in swine and humans [64]. A postantibiotic effect *vs S. aureus* of 2.3 and 1.8 h was observed for **U-100592** and **U-100766**, respectively [57].

In several *in vivo* studies carried out by Ford and coworkers [58] in the mouse, **U-100592** administered sq or po demonstrated activity comparable to sq vancomycin (for eight MRSA strains, ED_{50}=0.9-8.0 mg/kg), while **U-100766** was equivalent to, or slightly less active (ED_{50}=2.0-15 mg/kg, MRSA) than vancomycin. Against the following organisms, **U-100592** and **U-100766** had respective ED_{50} values of 1.9 and 4.7 mg/kg (*S. epidermidis*); 1.3 and 10.0 mg/kg (*E. faecalis*); 12.5 and 25.0 mg/kg (vancomycin-resistant *E. faecium);* and 1.2-11.7 and 2.5-3.8 mg/kg (penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*).

Table II. In Vitro Antibacterial Activity of Oxazolidinone Drug Candidates, MIC_{90} (μg/mL)

Organism	DuP 721[5]	DuP 105[5]	U-100592[6]	U-100766[6]
MSSA[1]	1-4	4-16	2-4	2-4
MRSA[2]	2-4	4-16	2-4	2-4
MSSE[3]	NT[9]	NT	1	2
MRSE[4]	NT	NT	1	2
Enterococci	2-8	16	1-2	1-4
S. pyogenes	NT	NT	1-2	2-4
S. pneumoniae	2	4	0.50-1	1-2
Corynebacterium spp.	NT	NT	0.50	0.50
H. influenzae	32	64	16	16
M. catarrhalis	NT	NT	4	4
B. fragilis	8 - 16	16	16	4
gram-(+) anaerobes	NT	NT	0.50-2	0.50-2
M. hyopneumoniae[7]	NT	NT	2.0	2.0
Mycoplasma spp.[8]	NT	NT	16	8

[1]Methicillin-sensitive *S. aureus*; [2]Methicillin-resistant *S. aureus*; [3]Methicillin-sensitive *S. epidermidis*; [4]Methicillin-resistant *S. epidermidis*; [5]Compilation of MIC_{90} data taken from [30,41,45,46,49] [6]Compilation of MIC_{90} data taken from [57,129-137] [7]respiratory pathogens of swine [147]; [8]Human pathogens

[8]Unpublished data, R.C. Piper, T.F. Platte, and J.R. Palmer, The Upjohn Company.

[9](*S*)-N-[[[3-[3-Fluoro-4-[N-1-(4-hydroxyacetyl)-piperazinyl]]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Activity Against *M. tuberculosis* and *M. Avium*

DuP 721 and DuP 105. DuP 105 was reported to have MICs of 0.3-1.25 μg/mL against *M. tuberculosis* [82]. The activity of **DuP 721** *vs* 25 clinical isolates of *M. tuberculosis* compared well with that of rifampin; MICs were 0.3-1.25 μg/mL, and 99.9% kill minimum bactericidal concentration [MBC] was 2.5 μg/mL [42]. **DuP 721** was found not to be cross-resistant [82,84], and attempts to select a resistant mutant were unsuccessful [82,83]. While the drug was inactive against *M. avium* and *M. intracellulare*, atypical mycobacterial pathogens had MICs of 1.9-15.6 μg/mL [85]. Antagonism with rifampin was seen *in vitro* [84,85].

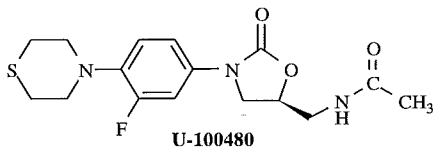
In mice infected with *M. tuberculosis*, an ED_{50} of 13.2 mg/kg (100% survival at 50 mg/kg) was observed, when (±)-**DuP 721** was administered daily for 17 days [85]. The increase in survival time was inferior to similar treatment with either rifampin or INH.

Structurally Unidentified Oxazolidinones

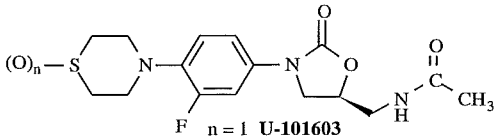
The activity of four structurally unidentified DuPont oxazolidinones *vs M. avium* complex [MAC] isolates from HIV-infected patients was reported [86]. The compounds E-3656-2, E-3709-5 (relation to **E-3709** not identified), and E-3556-2 had MICs= 0.5-4.9 μg/mL, while XA-043 (a more water soluble E-3709-5 derivative) was less active. Evidence for cross resistance with amikacin was reported.

U-100480, U-100766, and U-100592

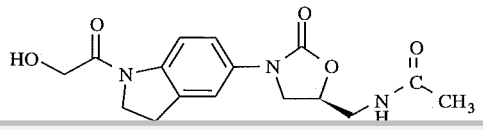
Barbachyn et al. [87] reported that substitution of a thiomorpholinyl ring for the morpholinyl ring of **U-100766** gave the very potent anti-tuberculosis drug **U-100480**. Kilburn et al. [87] identified **U-100480** and its sulfoxide metabolite **U-101603** as the most potent of the Upjohn oxazolidinones tested *vs M. tuberculosis* H37Rv, (MIC ≤0.125 μg/mL, *vs* the clinical benchmark INH, MIC=0.2 μg/mL). The corresponding sulfone **U-101244** (a minor metabolite of **U-100480**), **U-100592**, and **U-100766** [56] also exhibited potent activity (MIC_{80}s ≤ 0.50 μg/mL) *vs* a battery of five drug sensitive, and five multi-drug resistant strains of *M. tuberculosis*. In this battery, the racemate of 4'-indolinyl oxazolidinone **U-97456** [73,96] also demonstrated very good *in vitro* activity (MIC_{80} =1.0 μg/mL).



U-100480



n = 1 **U-101603**
n = 2 **U-101244**



Klemens and coworkers [88] reported on the po *in vivo* anti-tuberculosis activities of **U-100480** and **U-100766**, relative to INH in CD-1 mice infected with *M. tuberculosis* (MICs for **U-100480**, **U-100766** and **INH** were 1, 0.5, and 0.03 μg/mL, respectively). Treatment for four weeks with **U-100480** (at 100 mg/kg) gave comparable activity as **INH** (at 25 mg/kg), whereas **U-100766** was somewhat less active.

Cynamon et al. [89] evaluated **U-100480** and **U-100766**, relative to azithromycin (**AZI**), in beige mice infected with MAC (for all three drugs, the MIC=4 μg/mL). Drug was administered (po) for 10 days at 100 mg/kg. Spleen and lung cell counts showed **U-100480** to be more active than **U-100766**, but less active than **AZI**. Upon dosing for 4 weeks, **U-100480** and **AZI** at 100 mg/kg showed similar activity *vs* MAC in the lungs, but **AZI** was more active in the spleen.

Oxazolidinone Mechanism of Action Studies

DuP-721. DuP-721 has been extensively studied in attempts to elicit the mechanism of action of the oxazolidinones. The drug was shown to inhibit bacterial protein synthesis *via* a new mode of action, the details of which remain not well defined. Extensive work by Eustice and colleagues led them to surmise that "DuP 721 may inhibit recognition of the 3' upstream ribosome-binding sequence present in natural mRNAs" [65], i.e., acting at the Shine-Delgarno ribosomal recognition site [66]. **DuP 721** inhibited protein synthesis (IC_{50}=3.8 μg/mL) in an OmpF-mutant *E. coli* strain, but not DNA or RNA synthesis (IC_{50}>64 μg/mL) [65,67].

As has been subsequently found with other 5-acetamidomethyl-2-oxazolidinones, **DuP 721** is inactive *vs* wild-type *E. coli* [30] and other gram-negative aerobes. This resistance to **DuP 721** has been attributed to the gram-negative cell wall outer membrane [65]. Upon finding activity against *E. coli* permeability mutants, DuPont concluded the target site of action was the same for both gram-negative and gram-positive bacteria [65].

Addition of **DuP 721** to cell-free systems (using synthetic or natural mRNA templates) did not inhibit the stages of protein synthesis from chain initiation, through elongation. **DuP 721**-growth-arrested cells were found defective in initiation-dependent peptide synthesis directed by RNA from an MS2 bacteriophage. Extracts from those cells could elongate a peptide, yet were then unable to subsequently use natural mRNA for initiation of protein synthesis. Hence, it was concluded that **DuP 721** was acting at an early step of protein synthesis, one preceding the interaction of the fMet-tRNA and the 30S ribosome with the initiator codon [41,65].

Similar mechanistic studies with **S-6123** demonstrated that it also inhibited protein synthesis, but not RNA or DNA synthesis [34,35].

Bacteriostatic vs Bactericidal Nature of Oxazolidinones

Time-kill curve studies indicated that both **DuP 721** and **DuP 105** were bacteriostatic *vs*. all organisms tested, except

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