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New carbon-linked azole oxazolidinones with improved potency and pharmacokinetics

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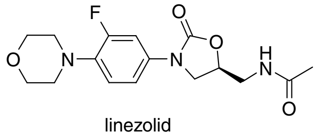
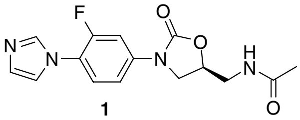
Abstract—Substitution of phenyl oxazolidinones with carbon-linked azoles resulted in the discovery of a new class of potent oxazolidinones that have excellent Gram-positive activity. In addition, replacement of the C-5 acetamide side chains with a 4-methyl triazole diminished monoamine oxidase activity. The synthesis and biological evaluation of these compounds are reported.

As a result of emerging multi-drug resistance to antibacterials, the search for new anti-infective agents is relentless. The oxazolidinones are one of the few new classes of antibacterials developed in the past thirty years. Originally discovered by Dupont scientists in the 1980s,[1] they have potent activity against Gram-positive organisms, including multi-drug resistant strains. Their mode of action involves the inhibition of protein synthesis at a unique binding site on the 50S ribosomal subunit.[2] However, oxazolidinone antibacterials, as a class, often exhibit undesirable side effects including bone marrow suppression and monoamine oxidase A (MAO-A) inhibition.[3] The MAO-A inhibition could potentially elevate blood pressure in conjunction with certain foods, or lead to drug–drug interactions;[4] therefore, it is important to discover oxazolidinones that do not exhibit this side-effect. Pfizer's linezolid (Zyvox®), launched in 2000, is useful against Gram-positive pathogens but is inactive against most Gram-negative organisms. Pfizer later reported that certain N-linked azole analogs **1** and **2** have moderate Gram-negative activity (*Haemophilus influenzae* minimum inhibitory concentrations {MICs} of 4–8 μg/ml).[5]



linezolid



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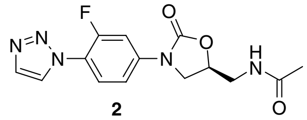

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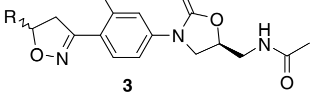
Johnson & Johnson reported the synthesis and activity of their 3-isoxazolinyl (**3**) and 3-isoxazolyl (**4**) oxazolidinone analogs shown below. Both series include compounds with activity against Gram-positive strains that is comparable to linezolid in vitro, but were found to be less efficacious in vivo; the authors attributed this to either insolubility in the vehicle or poor pharmacokinetics.[6]



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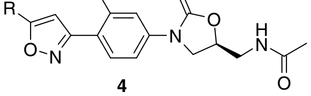

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In addition, Dong-A Pharmaceuticals described a series of 5-isoxazolyl derivatives such as **5** and **6** that have microbiological activity equal or superior to vancomycin.[7]

Keywords: Triazoles; Isoxazoles; Oxazolidionones.

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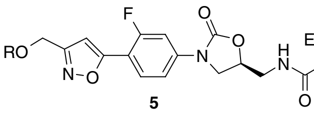

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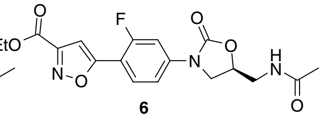

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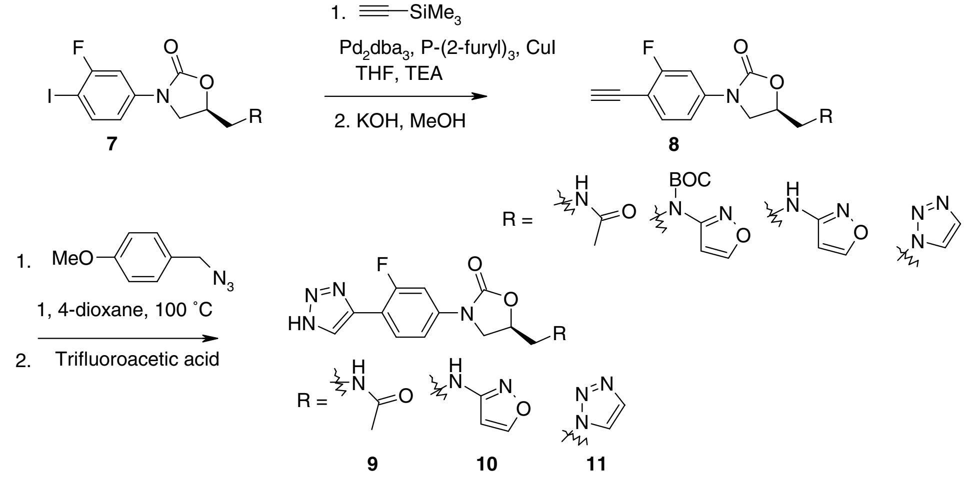
All of these compounds utilize the acetamide side chain because early structure–activity relationships had indicated it was required for potency.[8] We have previously demonstrated that the acetamide side chain in oxazolidinones can be replaced with five-membered heterocycles such as aminoisoxazoles, hydroxyisoxazoles, and triazoles, and still retain comparable activity.[9] More recently, we have disclosed that 4-substituted triazoles can diminish MAO-A inhibition.[10] In the course of our investigations to find a broader spectrum antibacterial, these heterocycles were studied in combination with various carbon-linked azole substituents on the phenyl ring, resulting in new antibacterials with exemplary microbiological potency and DMPK properties described here.

We initially examined substitution of the phenyl ring with carbon-linked triazoles in combination with our heterocyclic side chains using the route in Scheme 1.

A palladium-catalyzed Sonagashira coupling of trimethylsilyl acetylene with the iodophenyloxazolidinone **7** followed by removal of the silyl group gave the alkyne intermediate **8**.[11] Cycloaddition with *p*-methoxybenzyl azide gave a mixture of regioisomers, which, upon deprotection with neat trifluoroacetic acid, gave the carbon-linked triazoles **9**–**11**. The microbiological activity of a few examples is shown in Table 1.

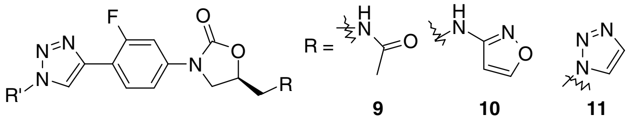
The carbon-linked triazoles **9**–**11** had disappointing antimicrobial potency against both Gram-positive and Gram-negative strains, less active than linezolid. Alkylation of the phenyl-triazole (compounds **12** and **13**) did not significantly improve activity. Subsequently, other carbon-linked azoles, such as isoxazoles, were investigated. The synthesis of the carbon-linked isoxazoles is shown in Scheme 2.

The isoxazolyl stannane **14** was prepared using a literature procedure for cycloaddition of nitrile oxides with tributylethynyl stannane.[12] Palladium-catalyzed Stille couplings gave the isoxazole oxazolidinones **15**–**18** in moderate to high yields. Removal of the Boc-protecting group from **16** gave compound **19**. Although the carbon-linked isoxazoles have only moderate Gram-negative activity compared to nitrogen-linked analogs, they



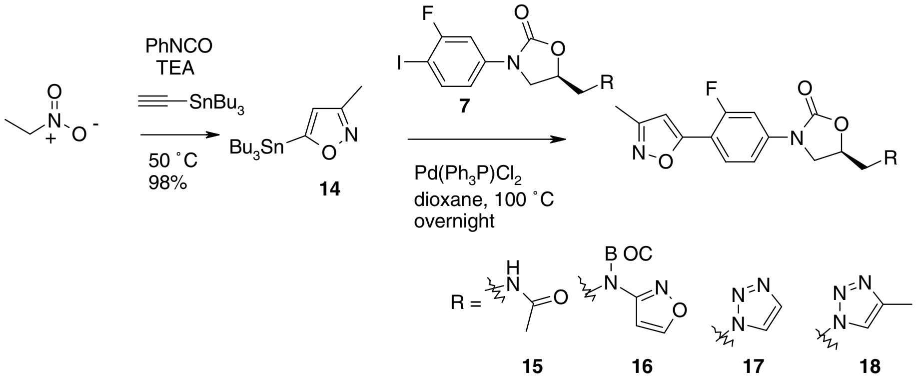
Scheme 1. Synthesis of carbon-linked triazole oxazolidinones.

Table 1. In vitro activity (μg/ml) of oxazolidinones **9**–**13**



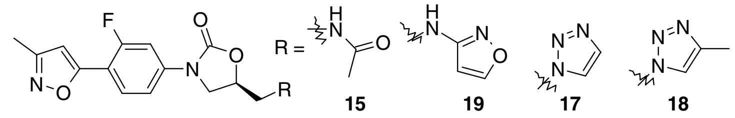
Compound	R	R′	Hin	Sau	Spn
9	Acetamide	H	8	4	2
10	Aminoisoxazole	H	16	8	16
11	Triazole	H	>64	64	32
12	Triazole	Me	>64	32	16
13	Triazole	Cyano-methyl	32	4	2
Linezolid			8	2	1

Hin, *Haemophilus influenzae*; Sau, *Staphylococcus aureus*; Spn, *Streptococcus pneumoniae*.



Scheme 2. Synthesis of carbon-linked isoxazole oxazolidinones.

Table 2. In vitro activity (μg/ml) and monoamine oxidase inhibition (μM) of oxazolidinones **15**–**19**



Compound	R	Hin	Sau	Spn	MAO-A K_i
15	Acetamide	4	0.5	0.25	0.95
19	Aminoisoxazole	16	0.5	0.25	0.42
17	Triazole	8	0.5	0.25	2.9
18	4-Methyl triazole	4	0.5	0.25	22.6
Linezolid		8	2	1	20

Hin, *Haemophilus influenzae*; Sau, *Staphylococcus aureus*; Spn, *Streptococcus pneumoniae*.

do have very potent Gram-positive activity relative to linezolid as shown in Table 2. In addition, the data in Table 2 demonstrate the decrease in monoamine oxidase potency as the right hand side chain is varied from aminoisoxazole to 4-methyltriazole.

The pharmacokinetic (PK) properties of two of these compounds (**17** and **18**) were evaluated in rat and the data are shown in Table 3. Both compounds have low clearance (Cl), low volume of distribution (V_{ss}), and a moderate half-life ($t_{1/2}$). The oral bioavailability (F) is quite good for both analogs.

Due to the excellent in vitro potency and PK properties seen in this series, selected compounds were further tested in vivo in a mouse lung infection model against *Streptococcus pneumoniae*. The data are shown in Figure 1 versus the vehicle and linezolid for comparison. While the reduction of bacterial colony forming units (CFU) by compounds **15** and **19** was unexpectedly low (22% and 33%, respectively) relative to linezolid (75%), compound **17** was extremely efficacious, yielding a 92% CFU reduction.

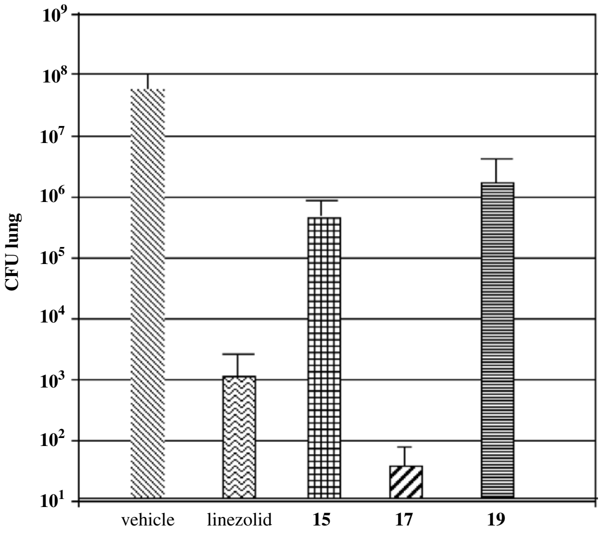


Figure 1. Efficacy of linezolid, **15**, **17**, and **19** in mice after *Streptococcus pneumoniae* lung infection and three doses (25 mg/kg po) of each compound.

Table 3. Pharmacokinetic parameters of oxazolidinones **17** and **18** in rat

Compound	Cl (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	F (%) 40 mg/kg
17	5	0.6	1.7	82
18	5	0.5	1.2	87

In conclusion, we report the synthesis[13] and biological evaluation of a new class of oxazolidinones. The 3-methylisoxazole-phenyl oxazolidinones have excellent Gram-positive activity and DMPK properties. In particular, compound **17** shows exceptional efficacy against *S. pneumoniae* infections. Replacement of the typical acetamide group by 4-methyl triazole showed diminished MAO-A inhibition in our series. Additional work exploring the substitution of the isoxazole ring is ongoing in order to improve the Gram-negative activity.

In vitro and in vivo assays. The bacteria used in these studies were taken from the AstraZeneca culture collection. Minimum inhibitory concentrations were generated by broth microdilution according to the Clinical and Laboratory Standards Institute guidelines[14] for the majority of bacteria. Human liver monoamine oxidase-A activity was assayed by adapting the method of Flaherty.[15] The K_i is expressed as a mean of three experiments. Specific conditions were: 100 mM substrate 4-(1-methyl-2-pyrryl)-1-methyl-1,2,3,6-tetrahydropyridine, 82 nM human liver monoamine oxidase A, 100 mM potassium phosphate buffer, pH 7.4, and 25 °C. The mouse efficacy model experimental design utilized the following protocol: *S. pneumoniae* ARC548 was administered at 1×10^6 CFU to anesthetized female C57BL/6 mice. Eighteen hours after infection, experimental compounds were administered orally at 25 mg/kg, each mouse received two additional administrations at 4-h intervals. Mice were sacrificed and total CFU/lung were determined 2 days after infection.

Acknowledgments

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