Sonication-Assisted Library Synthesis of Oxazolidinone−Carbohydrate Conjugates

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Oxazolidinone derivatives have attracted growing interest in their pharmacological applications.[1] Linezolid (or Zyvox), for example, is the first FDA approved antibacterial drug in over 30 years (Figure 1).[2] The novel mechanism of action[3]

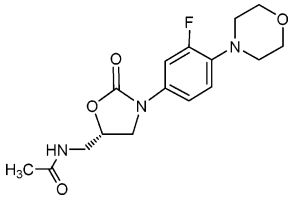


Figure 1. Structure of linezolid.

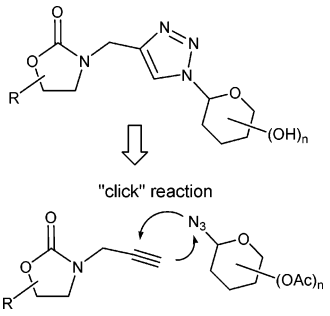


Figure 2. Retrosynthetic analysis.

of linezolid has prompted further effort in chemical modifications and structure−activity relationship (SAR) studies.[4]

Carbohydrates have the advantage of introducing multiple functionalities in a single chemical step; thus they receive escalating attention for their use in the development of therapeutics.[5] Recently, the "click" reaction between an azido group and an alkyne has been heavily investigated because of its simplicity in coupling diverse molecular moieties.[6] Thus, we began to ponder the creation of carbohydrate derivatives conjugated with oxazolindinones using click chemistry as potentially novel antibacterial therapeutics.

The designed molecules contain an oxazolidinone and a triazole ring, which could be a mimic of the benzene ring

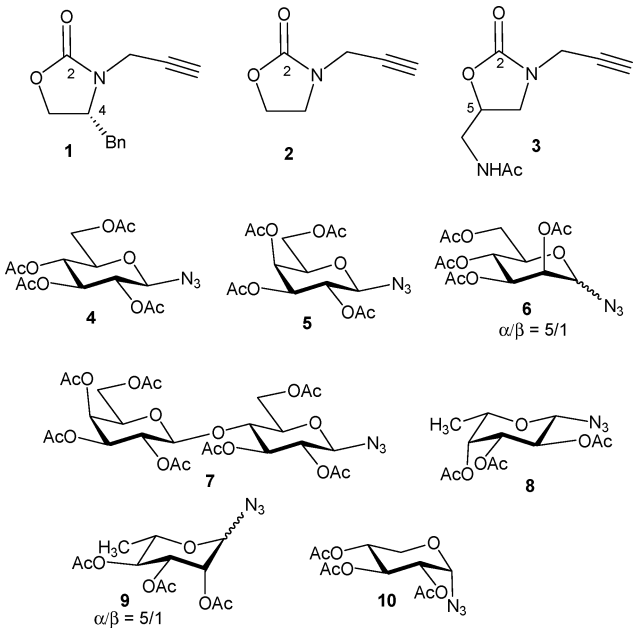
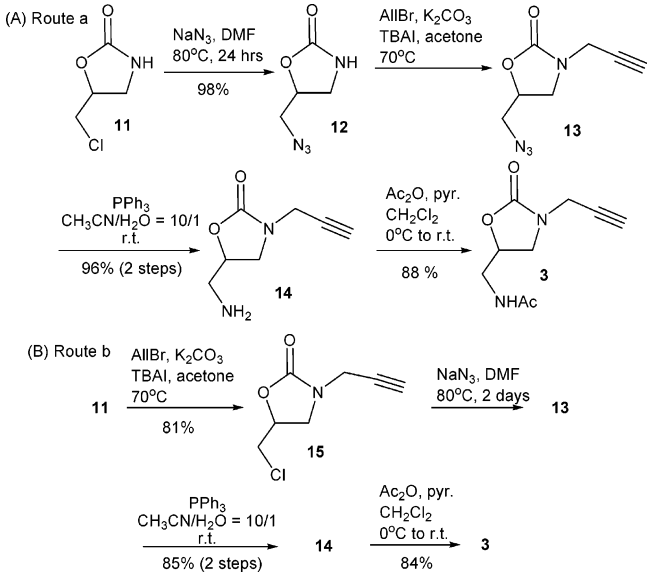
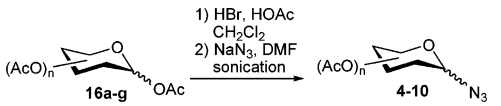


Figure 3. Structure of selected oxazolidinone and azidosugar moieties.

Scheme 1. Synthesis of **3**



Scheme 2. Synthesis of Azidosugars



Compounds	Carbohydrate Moiety	Yield (%)	α/β
4[s]	Tetra-*O*-acetyl-D-glucopyranosyl	38	β only
5[s]	Tetra-*O*-acetyl-D-galactopyranosyl	73	β only
6[s]	Tetra-*O*-acetyl-D-mannopyranosyl	12	5/1
7[†]	4-*O*-(Tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-D-glucopyranosyl	79	β only
8	Tri-*O*-acetyl-β-L-fucopyranosyl	66	β only
9[s]	Tri-*O*-acetyl-L-rhamnopyranosyl	44	5/1
10	Tri-*O*-acetyl-D-xylopyranosyl	47	α only

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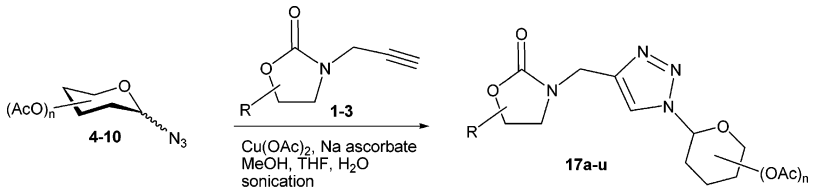
Scheme 3. Structure of Selected Oxazolidinone and Azidosugar Moieties



Compounds	R	Azidosugars	Yield (%)	α/β
17a	(*R*) 4-Bn	**4**	80	β only
17b	(*R*) 4-Bn	**5**	99	β only
17c	(*R*) 4-Bn	**6**	86	5/1
17d	(*R*) 4-Bn	**7**	70	β only
17e	(*R*) 4-Bn	**8**	99	β only
17f	(*R*) 4-Bn	**9**	48	3/1
17g	(*R*) 4-Bn	**10**	96	10/1
17h	H	**4**	75	β only
17i	H	**5**	99	β only
17j	H	**6**	82	10/1
17k	H	**7**	95	β only
17l	H	**8**	43	β only
17m	H	**9**	67	α only
17n	H	**10**	80	α only
17o	5-AcNHCH$_2$-	**4**	92	β only
17p	5-AcNHCH$_2$-	**5**	95	β only
17q	5-AcNHCH$_2$-	**6**	86	5/1
17r	5-AcNHCH$_2$-	**7**	88	β only
17s	5-AcNHCH$_2$-	**8**	99	β only
17t	5-AcNHCH$_2$-	**9**	90	2/1
17u	5-AcNHCH$_2$-	**10**	99	α only

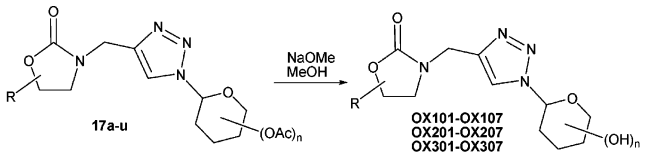
found in linezolid (Figure 2). The carbohydrate component can be viewed as a surrogate of the morpholine of linezolid. Pyranoses have the same six-membered ring scaffold as morpholine. In addition, the readily accessible structural varieties and the hydroxyl groups of carbohydrates can provide prompt evaluation and probing for advantageous activity. We selected three oxazolidinone-containing compounds and seven 1-azidosugars for our initial attempt (Figure 3).

Compounds **1** and **2** can be prepared by allylation of commercially available (*R*)-4-benzyl-2-oxazolidinone and 2-oxazolidinone, respectively. Compound **3** can be synthesized from commercially available 5-chloromethyl-2-oxazolidinone, **11** (Scheme 1). Two individual routes were developed by alternation of the order of azide substitution and allylation. However, the approach that has azide substitution first provides better overall yield in larger-scale synthesis. The other approach that goes through allylation first suffered from a low yield in the following azide substitution (from **15** to **13**) when scaled up, despite having a prominent yield in small-scale test reaction.

The synthesis of azido glycosides often requires the use of $TMSN_3$ catalysized by a Lewis acid for several hours.[7] This is a lengthy and expensive procedure. My research group has discovered that sonication can facilitate various types of chemical reactions.[8] For example, the azido group of azidosugars can be installed via the corresponding glycosyl bromides in minutes.[9] The time for the desired click reaction can be shortened from days to less than 15 min with excellent regioselectivity. After hydrolysis of the acetyl groups and purification with flash column chromatography, the molecules can be obtained in modest to excellent overall yields (Schemes 2−4).

Using the disk diffusion assay methods described by Grgurina et al.[11] and NCCLS,[12] we tested the compounds for inhibition of various strains of bacteria, including *Escherichia coli* (ATCC25922), *Staphylococcus aureus* (ATCC25923), and *Mycobacterium smegmatis* (ATCC 14468), and two strains of fungi, *Rhodotorula pilimanae*[13] and *Rhototorula rubra* (ATCC 9449). No inhibitory activities were observed. The lack of activity is consistent with the reported SAR, which states that an N-aryl group is essential for activity. The synthesis for linezolid analogs with a triazole ring connected directly to the oxazolidinone (N-aryl-type linkage) has been initiated. Although we did not obtain any antimicrobial activity with the newly constructed oxazolidinone−carbohydrate conjugates, the concise synthetic strat-

Scheme 4. Structure of Selected Oxazolidinone and Azidosugar Moieties



Compounds	R	Carbohydrate Moiety	Yield (%)	α/β
OX101	(*R*) 4-Bn	D-glucopyranosyl	82	β only
OX102	(*R*) 4-Bn	D-galactopyranosyl	99	β only
OX103	(*R*) 4-Bn	D-mannopyranosyl	99	5/1
OX104	(*R*) 4-Bn	4–*O*-(β-D-galactopyranosyl)-D-glucopyranosyl	95	β only
OX105	(*R*) 4-Bn	β-L-fucopyranosyl	90	β only
OX106	(*R*) 4-Bn	L-rhamnopyranosyl	98	5/1
OX107	(*R*) 4-Bn	D-xylopyranosyl	96	α only
OX201	H	D-glucopyranosyl	99	β only
OX202	H	D-galactopyranosyl	99	β only
OX203	H	D-mannopyranosyl	82	7/1
OX204	H	4–*O*-(β-D-galactopyranosyl)-D-glucopyranosyl	99	β only
OX205	H	β-L-fucopyranosyl	99	1/20
OX206	H	L-rhamnopyranosyl	93	20/1
OX207	H	D-xylopyranosyl	95	α only
OX301	5-AcNHCH$_2$-	D-glucopyranosyl	89	β only
OX302	5-AcNHCH$_2$-	D-galactopyranosyl	99	β only
OX303	5-AcNHCH$_2$-	D-mannopyranosyl	95	5/1
OX304	5-AcNHCH$_2$-	4–*O*-(β-D-galactopyranosyl)-D-glucopyranosyl	99	β only
OX305	5-AcNHCH$_2$-	β-L-fucopyranosyl	99	β only
OX306	5-AcNHCH$_2$-	L-rhamnopyranosyl	55	20/1
OX307	5-AcNHCH$_2$-	D-xylopyranosyl	86	α only

egy and the efficiency of using sonication can pave the way for facile preparation of novel oxazolidinone-containing molecules.

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Supporting Information Available. ^{1}H and ^{13}C spectra of the synthesized compounds and the experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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