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Synthesis and structure–activity studies of novel benzocycloheptanone oxazolidinone antibacterial agents

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Abstract—We describe a novel class of benzocycloheptanone derived oxazolidinone antibacterial agents. The synthesis and antibacterial activities with structure variation is discussed.
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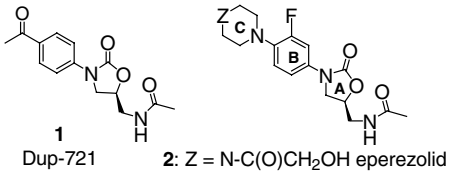
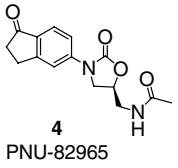
Oxazolidinones are a new class of totally synthetic antibiotics with excellent activity against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), and vancomycin-resistant enterococci (VRE).[1] This class of compounds (e.g., **1**, Dup-721) was initially discovered at E.I. du Pont Nemours & Company in the 1980s.[2] Later, extensive structure–activity relationship (SAR) efforts at Pharmacia and Upjohn led to eperezolid (**2**) and linezolid (**3**) as clinical candidates.[3] Subsequently, the food and drug administration (FDA) approved linezolid (ZYVOX®) for the treatment of community-acquired and nosocomial pneumonia, complicated and uncomplicated skin and soft-tissue infections, and infections caused by MRSA and VRE.

Previous SAR studies at Du Pont and Pharmacia also led to the indanone analog (PNU-82965, **4**)[4] possessing Gram-positive antibacterial activity. Herein, we report the synthesis and antibacterial activities of ketone analogs of various ring sizes, including benzocycloheptane analogs possessing functional groups at various positions on the seven-membered ring and also substitutions on the phenyl ring. Notably, these compounds lack the typical C-ring as present in linezolid.





The oxazolidinone containing a tetralone moiety (**5**) was synthesized in two steps as shown in Scheme 1. The first step is a copper catalyzed coupling[5] of oxazolidinone fragment **7** with 7-bromo-3,4-dihydro-2*H*-naphthalene-1-one **6**, followed by deprotection of the dimethoxybenzyl group in **8** to afford the oxazolidinone **5**.

Keywords: Oxazolidinones; Antibacterial agents; Gram-negative activity.
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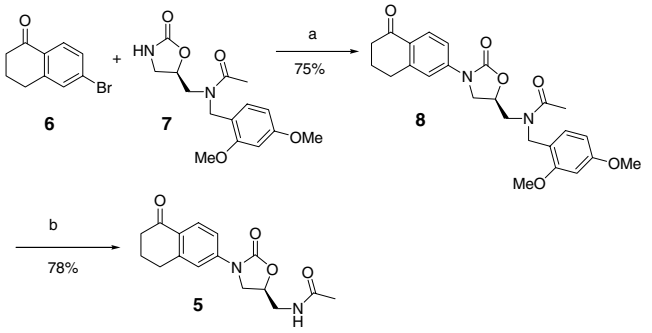
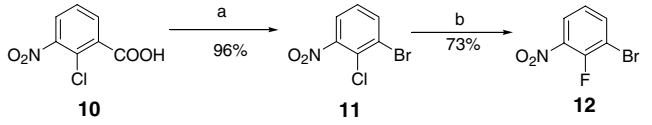
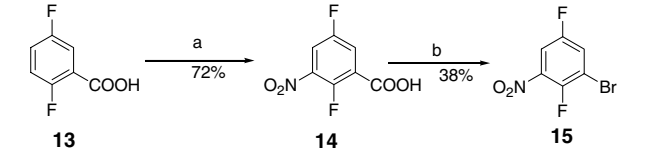


Scheme 1. Reagents: (a) *trans*-1,2-diaminocyclohexane, CuI, potassium carbonate; (b) trifluoroacetic acid.



Scheme 2. Reagents and condition: (a) Br_2, HgO, CCl_4, light; (b) KF/CsF, DMF.

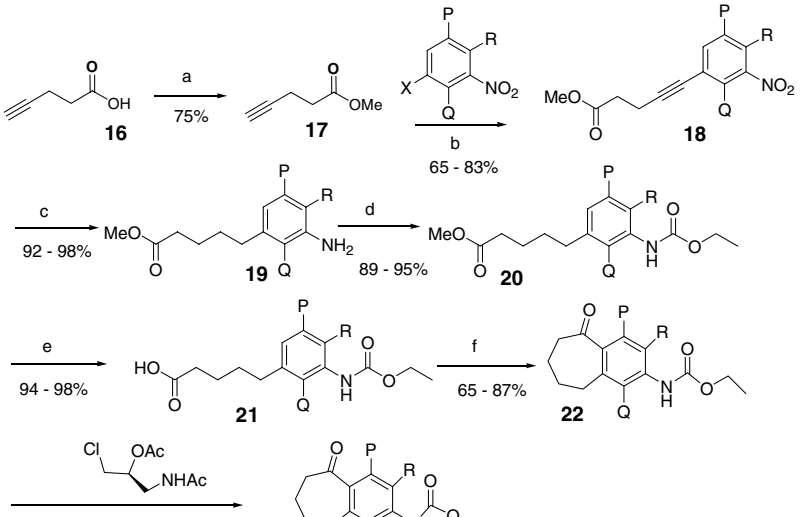


Scheme 3. Reagents: (a) nitric acid, sulfuric acid; (b) Br_2, HgO, CCl_4, light.

Benzoheptanone oxazolidinones (**9**) were synthesized in a multi-step procedure as shown in Scheme 4.[6] The intermediates required for Sonogashira coupling were synthesized as shown in Schemes 2 and 3. The remaining nitro compounds are commercially available.

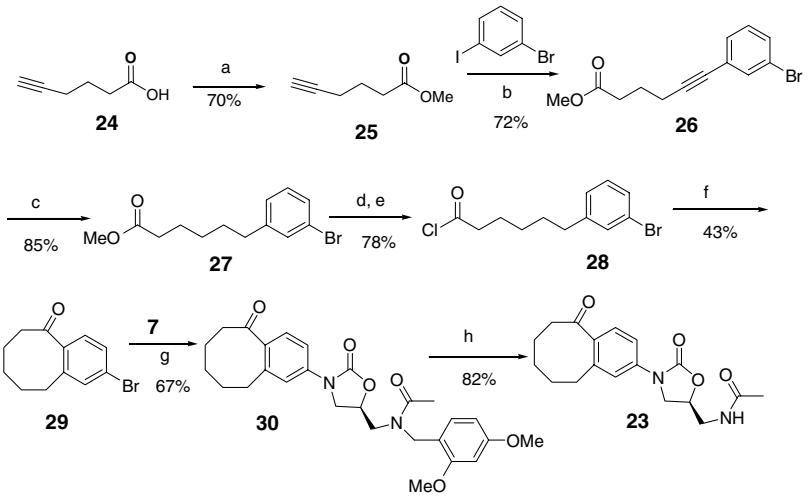
4-Pentynoic acid (**16**) on treatment with methanol in the presence of acid gave its methyl ester **17**. Coupling with the corresponding 1-iodo- or 1-bromo-3-nitrobenzene under Sonogashira coupling conditions[7] afforded compound **18**. The nitro group in **18** was reduced to the amine moiety (**19**), followed by reaction with ethyl chloroformate to afford the corresponding ethyl carbamate **20**. The ester group in **20** was saponified to the corresponding acid **21**. Intramolecular cyclization of **21** under acidic conditions furnished benzocycloheptanone **22**. Next, the C-5 acetamidomethyl oxazolidinone side chain in **9** was installed in a single step by using (1*S*)-2-(acetylamino)-1-(chloromethyl)ethyl acetate.[8] Some of these intermediates (**22**) were synthesized in multi-gram (20–200 g) quantities without any scale-up issues.

An oxazolidinone possessing a benzooctanone moiety (**23**) was synthesized using hex-5-ynoic acid **24** as the starting material (Scheme 5). The methyl ester of **25**, on coupling with 1-iodo-3-bromobenzene, afforded the compound **26**. Triple bond reduction in **26**, then saponification of the ester group in **27** followed by conversion of the acid to the acid chloride afforded compound **28**. Intramolecular cyclization of **28** in the presence of aluminum chloride under high dilution conditions, as described by Allinger et al., gave **29**.[9] Coupling of **29**



9a:P= Q= R = H
9b: P = F, Q = R =H
9c: P =R = H, Q =F
9d:P= Q= H, R = F
9e: P = Q = F, R=H

Scheme 4. Reagents: (a) sulfuric acid, MeOH; (b) appropriately substituted 1-iodo- or 1-bromo-3-nitrobenzene, $Pd(OAc)_2$, triphenylphosphine, CuI, diethylamine, DMF; (c) 10% Pd/C, H_2, MeOH; (d) ethyl chloroformate, diisopropylamine, CH_2Cl_2; (e) 2 N LiOH, MeOH, THF; (f) P = Q = R = H: polyphosphoric acid, toluene, Celite; others: phosphorus pentoxide, methanesulfonic acid; (g) lithium *tert*-butoxide in hexanes, DMF.



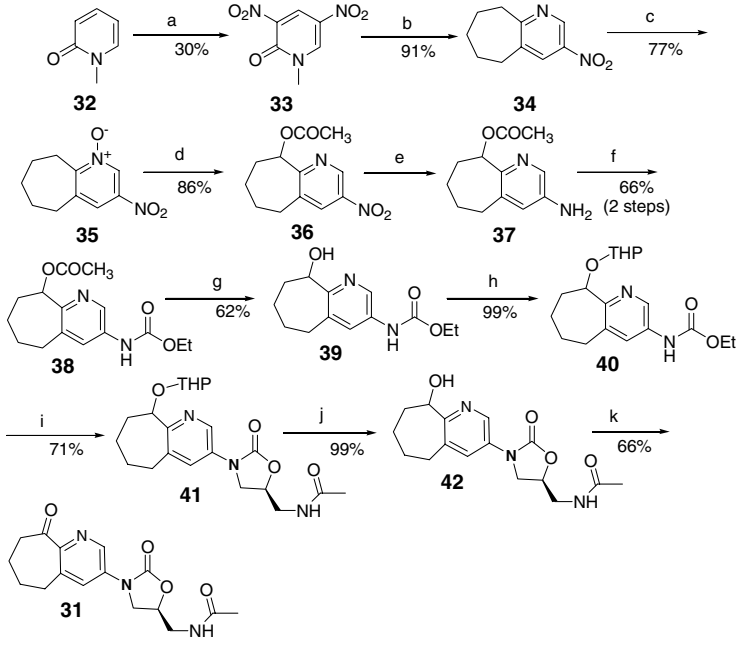
Scheme 5. Reagents: (a) sulfuric acid, MeOH; (b) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF; (c) Raney nickel, H_2, MeOH; (d) NaOH, MeOH; (e) oxalyl chloride, benzene, catalytic amount of DMF; (f) $AlCl_3$, CS_2; (g) *trans*-1,2-diaminocyclohexane, CuI, potassium carbonate; (h) trifluoroacetic acid.

with **7** yielded **30**, followed by deprotection, giving the final oxazolidinone **23**.

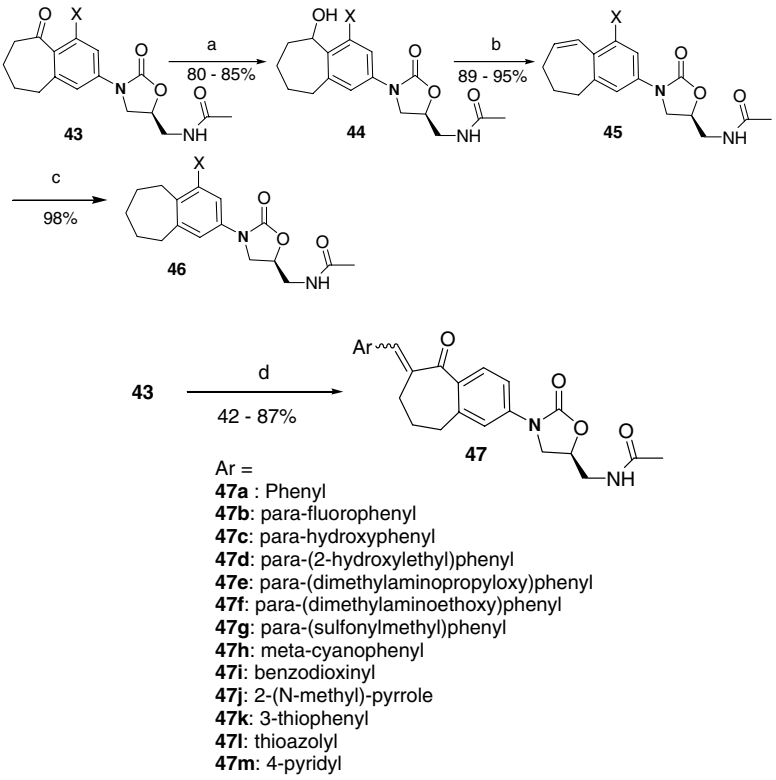
Pyridylbenzoheptanone analog (**31**) was synthesized as shown in Scheme 6 starting from *N*-methylpyridone (**32**). The first step was nitration to **33**. Condensation with heptanone yielded **34**,[10] which on further treatment with MCPBA afforded the corresponding *N*-oxide (**35**). Pummerer-like rearrangement of **35** gave **36**.[11] Reduction of the nitro group, followed by amino group protection, yielded the corresponding ethyl carbamate **38**. Saponification of the acetate group and protection of the alcohol group as a THP ether gave **40**. Oxazolidinone ring formation was accomplished in one step under basic conditions by treating **40** with (1*S*)-2-(acetylamino)-1-(chloromethyl)ethyl acetate. Deprotection of the THP ether (**41**) to the corresponding alcohol (**42**), followed by oxidation, furnished the final ketone **31**.

Oxazolidinones containing a substituted benzocycloheptane moiety were synthesized as shown in Scheme 7.

These novel oxazolidinone analogs were tested against a panel of Gram-positive and fastidious Gram-negative bacteria.[12] Minimum inhibitory concentration (MIC) of the test compounds was determined by micro broth methodology according to the Clinical



Scheme 6. Reagents: (a) nitric acid, sulfuric acid; (b) cycloheptanone, ammonia, MeOH; (c) MCPBA, CH_2Cl_2; (d) Ac_2O; (e) $SnCl_2$, EtOAc; (f) ethyl chloroformate, pyridine; (g) K_2CO_3, MeOH, H_2O; (h) dihydropyran, PTS; (i) LiO-*t*-Bu, MeOH, DMF; (j) PTS, MeOH; (k) oxalyl chloride, DMSO, CH_2Cl_2.



Scheme 7. Reagents: (a) $NaBH_4$; (b) PPTS; (c) Pd/C, H_2; (d) ArCHO, piperidine.

and Laboratory Standards Institute Guidelines (Formerly, National Committee for Clinical Laboratory Standards, NCCLS). The *Escherichia coli* in vitro transcription and translation (TnT) assay was performed in 96-well microtiter plates using a luciferase reporter system.[13]

Table 1 shows the effect of ring size on antibacterial activities. Analogs possessing a seven-membered ring system, for example, **9a** showed better antibacterial activities than their five (**4**), six (**5**), and eight (**23**) membered ring congeners. Compound **9a** also showed better antibacterial activities compared to the acyclic system

Table 1. Minimum inhibitory concentrations (MICs) for ketones possessing various ring sizes

Compound	EC TnT IC_{50} (μM)	S. a. MIC (μg/mL)	S. p. MIC (μg/mL)	S. py. MIC (μg/mL)	E. f. MIC (μg/mL)
3 linezolid	3.3 ± 0.46	2	2	1	2
1 (Dup-721)	7.5 ± 0.83	2	2	1	2
4	21 ± 2.9	8	2	2	8
5	4 ± 0.29	32	8	16	16
9a	3.9 ± 0.18	1	0.5	0.5	0.5
23	5.9 ± 0.72	4	4	2	8

Strains: S. a., *Staphylococcus aureus* UC-76 SA-1; S. p., *Streptococcus pneumoniae* SVI SP-3; S. py., *Streptococcus pyogenes* C-203, SP1-1; E. f., *Enterococcus faecalis* MGH-2 EF1-1.

Table 2. Minimum inhibitory concentrations (MICs) for ketones possessing various substitutions on the phenyl ring

Compound	EC TnT IC_{50} (μM)	S. a. MIC (μg/mL)	S. p. MIC (μg/mL)	S. py. MIC (μg/mL)	E. f. MIC (μg/mL)
3 linezolid	3.3 ± 0.46	2	2	1	2
9a	3.9 ± 0.18	1	0.5	0.5	2
9b	9.4 ± 1.2	8	2	2	4
9c	8.9 ± 0.73	16	4	8	8
9d	90 ± 5.5	64	32	32	64
9e	14 ± 1.5	32	8	16	16
31	13 ± 1.2	8	16	4	8

Strains: S. a., *Staphylococcus aureus* UC-76 SA-1; S. p., *Streptococcus pneumoniae* SVI SP-3; S. py., *Streptococcus pyogenes* C-203, SP1-1; E. f., *Enterococcus faecalis* MGH-2 EF1-1.

Table 3. Minimum inhibitory concentrations (MICs) for Benzocycloheptane analogs

Compound	EC TnT IC_{50} (μM)	S. a. MIC (μg/mL)	S. p. MIC (μg/mL)	S. py. MIC (μg/mL)	E. f. MIC (μg/mL)
3 linezolid	3.3 ± 0.46	2	2	1	2
45 (X = H)	1.3 ± 0.07	1	0.5	0.5	1
45 (X = F)	9.3 ± 0.59	2	1	1	2
46 (X = H)	8 ± 0.33	64	8	2	>64

Strains: S. a., *Staphylococcus aureus* UC-76 SA-1; S. p., *Streptococcus pneumoniae* SVI SP-3; S. py., *Streptococcus pyogenes* C-203, SP1-1; E. f., *Enterococcus faecalis* MGH-2 EF1-1.

Table 4. Minimum inhibitory concentrations (MICs) for α,β-unsaturated ketones

Compound	EC TnT IC_{50} (μM)	S. a. MIC (μg/mL)	S. p. MIC (μg/mL)	E. f. MIC (μg/mL)	H.i. MIC (μg/mL)	M. c. MIC (μg/mL)
3 linezolid	3.3 ± 0.46	2	2	1	16	8
47a	2.7 ± 0.4	1	0.25	0.5	16	4
47b	2.7 ± 0.13	0.5	0.25	0.5	2	2
47c	0.95 ± 0.13	0.5	0.125	0.5	8	2
47d	2.6 ± 0.4	1	0.25	0.5	16	4
47e	1.2 ± 0.11	1	0.125	0.5	16	4
47f	1.5 ± 0.07	2	0.25	2	32	8
47g	2.8 ± 0.24	1	0.25	0.5	16	4
47h	1.7 ± 0.1	0.5	0.25	0.25	32	2
47i	1.6 ± 0.08	0.5	0.25	0.25	8	1
47j	1.6 ± 0.27	1	0.25	0.5	16	4
47k	1.1 ± 0.22	2	0.125	0.5	2	1
47l	1.1 ± 0.16	1	0.25	0.5	16	4
47m	1.7 ± 0.2	1	0.5	1	16	8

Strains: S. a., *Staphylococcus aureus* UC-76 SA-1; S. p., *Streptococcus pneumoniae* SVI SP-3; E. f., *Enterococcus faecalis* MGH-2 EF1-1; H.i. *Haemophilus influenzae* HI-3542; M. c., *Moraxella catarrhalis* BC-3531.

(**1**) as well as linezolid (**3**). These analogs did not show fastidious Gram-negative activity when tested up to the maximum concentration of 64 μg/mL.

The phenyl ring of **9** was substituted with fluorine atoms at various positions, because such substitutions have showed enhanced activities in other series.[1,5] Various fluoro substitutions on the phenyl ring (series **9**), as well as replacing the phenyl ring with a pyridyl ring (**31**), did not enhance antibacterial activities (Table 2). Among the various benzocycloheptane analogs tested, compound **45** showed antibacterial activities similar to **9a** (Table 3).

Various analogs of **47** showed improved Gram-positive activities compared to linezolid. More significantly, **47b** and **47k** showed surprisingly potent activity against the fastidious Gram-negative organisms (Table 4). These results are a major improvement compared to the activities of linezolid versus fastidious Gram-negative bacteria. All of these analogs in Table 4 showed activities similar to or better than linezolid in the translation assay, thereby confirming the mechanism of action, that is, similar to linezolid.

In summary, novel oxazolidinones possessing various benzocycloalkyl rings were prepared and evaluated for antimicrobial activity. The analog possessing a benzocycloheptanone ring (**9a**) showed better antibacterial activities compared to other cycloketone analogs. More importantly, oxazolidinones of structure **47** also showed fastidious Gram-negative activities. The improved spectrum of antibacterial activities and novel analogs such as **47b** and **47k** represent promising new leads in the oxazolidinone area.

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