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

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Abstract—A novel series of oxazolidinones were synthesized in which the morpholine C-ring of linezolid was replaced with homomorpholine. In addition to investigating the effect of a homomorpholine C-ring on antibacterial activity, the effect of des-, mono-, di-, and tri-fluoro substitution on the phenyl B-ring was investigated as well. Various C-5 functional groups were also examined, including acetamides and triazoles and carboxamides. © 2008 Elsevier Ltd. All rights reserved.

Oxazolidinones are a new class of totally synthetic antibiotics with activity against Gram-positive organisms such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE).¹ Linezolid (ZyvoxTM) **1** is the first drug of this class to be approved for the treatment of infections caused by such serious Gram-positive bacteria.^{2,3} In an effort to investigate and expand the utility of oxazolidinones as antibacterial agents, a series of analogs were synthesized in which the morpholine C-ring of linezolid was replaced with a homomorpholine ring as shown in structures 2-4. The effect of the homomorpholine ring on antibacterial activity in comparison to that of linezolid was examined, as well as the effect of des-, mono-, di-, and tri-fluoro phenyl B-ring substitution (2-4: X, Y, Z = H; F) in the context of analogs with C-5 amides (2, $R^1 = NHAc$, NHCOEt). While investigating diverse functionalities at the C-5 position, it was brought to our attention that a number of oxazolidinone compounds with the 1,2,3-triazole moiety at the C-5 position reduced monoamine oxidase inhibition, a known side effect of oxazolidinones, while maintaining potency comparable to that of linezolid.⁴ It was therefore of interest to see if the potency was maintained with homomorpholine analogs with the triazole moieties (3, $R^1 = H$,

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CCH). It was also noted that recently reported oxazolidinone analogs with a novel C-5 carboxamide side chain achieved improved myelotoxicity.⁵ Thus, homomorpholine analogs with the novel side chain (4, $R^1 = H$, Me) were synthesized in addition to investigate the effect of such C-5 moiety on the antibacterial potency. The synthesis and the antibacterial activity of our novel homomorpholine analogs are reported here.



The synthesis of the C-5 acetamide analogs of the homomorpholine series is shown in Scheme $1.^6$ Homomorpholine hydrochloride was reacted with 4-fluoronitrobenzene (**5a**), 3,4-difluoronitrobenzene (**5b**), 3,4,5tri-fluorobenzene (**5c**), and 3,4,5,6-tetrafluoronitroben-

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Scheme 1. Reagents and conditions: (a) homomorpholine hydrochloride, (*i*-Pr)₂NEt; for **5a**, NMP, 50 °C; for **5b** and **5d**, NMP, -20 °C; for **5c**, CH₃CN, 0 °C; 88–100%; (b) Raney Ni, H₂, THF, 50 psi, 95–100%; (c) CbzCl, pyr, CH₂Cl₂, rt, 70–100%; (d) (2*S*)-3-acetamido-1-chloropropan-2-yl acetate **12**, *t*-BuOLi, DMF, 0 °C, 17–62%.

zene (5d) to give the corresponding des-, mono-, di-, and tri-fluoro nitroarene intermediates 6a-d, respectively.⁷ Subsequently following the reduction, the amine functionality in anilines 7a-d was protected as a benzyl carbamate (8a-d). The benzyl carbamates 8a-d were then reacted with (2S)-3-acetamido-1-chloropropan-2-yl acetate 12 and lithium *tert*-butoxide in DMF to result in the formation of both the oxazolidinone ring and the C-5 acetamide side chain in a single step (2a-d).

The preparation of the C-5 ethyl amides (20,p) and the C-5 carbamate analogs (2m,n) was achieved by first forming the *tert*-butyl carbamate intermediates 2e-h by reacting the benzyl carbamates 8a-d with (2*S*)-*tert*-butyl 3-chloro-2-hydroxypropyl carbamate 13 and lithium *tert*-butoxide in DMF. The *tert*-butyl carbamates 2e-h were then cleaved with hydrogen chloride. The resulting hydrochloride salts 2i-l were converted to the C-5 methyl carbamates 2m,n by treatment with methyl chloroformate or to the C-5 ethyl amides 20,p with propionic anhydride, respectively (see Scheme 2).

The synthesis of the C-5 triazole analogs (3a-d) is shown in Schemes 3 and 4.^{4,8} Starting from the benzyl carbamates **8a** and **8c**, oxazolidinones **2q,r** were prepared by treatment with (2R)-glycidyl butryrate and *n*-butyllithium. This step led to the closure of the oxazolidinone ring and cleavage of the resulting butyric ester in onepot to form the C-5 primary alcohols. The C-5 primary alcohol intermediates were converted to mesylates **9a,c** and then to the azide intermediates **10a,c**. Subsequently, the azides were reacted with bicyclo[2.2.1]hepta-2,5diene to provide the desired oxazolidinones with C-5 triazole **3a,b**.

The conversion of C-5-azidomethyl-3,5-difluorophenyloxazolidinone **10c** to the corresponding ethynyltriazolo-3,5-difluorophenyl-oxazolidinone **3d** was carried out utilizing a regioselective Cu(I) catalyzed cycloaddition as illustrated in Scheme 4.⁸ The transformation of azide **10c** to the trimethylsilyl protected ethynyl triazole **3c** was carried out efficiently with trimethylsilyl 1,3-butadiyne, 2,6-lutidine and copper iodide with excellent



Scheme 2. Reagents and conditions: (a) (2*S*)-*tert*-butyl 3-chloro-2-hydroxypropyl carbamate 13, *t*-BuOLi, DMF, 0 °C, 39–97%; (b) 4 M HCl in dioxane, THF, 0 °C, 48–100%; (c) for 2m,n, NaHCO₃, methyl chloroformate, THF/H₂O, rt; for 2o,p, NaHCO₃, propionic anhydride, THF/H₂O, rt; 85–95%.



Scheme 3. Reagents and conditions: (a) (2*R*)-glycidyl butryrate, *n*-BuLi, THF, -78 °C, 47-82%; (b) NEt₃, MsCl, CH₂Cl₂, 0 °C, 100\%; (c) NaN₃, DMF, 75 °C, 84–100\%; (d) bicyclo[2.2.1]hepta-2,5-diene, dioxane, 101 °C (reflux), 18–47\%.



Scheme 4. Reagents and conditions: (a) TMS-1,3-butadiyne, 2,6-lutidine, CuI, CH₃CN, rt, 62%; (b) KOH, MeOH, rt, 92%.

regioselectivity. No 1,5-regioisomers were detected in this reaction. The TMS group in **3c** was then cleaved with potassium hydroxide to give the desired C-5 ethy-nyl triazolo-3,5-difluorophenyl-oxazolidinone **3d**.

The synthesis of C-5 carboxamide analogs (4a-h) is shown in Scheme 5. The resulting anilines were reacted with (2R)-methyl glycidate followed by treatment with 1,1'-carbonyldiimidazole to afford the corresponding oxazolidinone C-5 methyl ester intermediates 11a-d.



Scheme 5. Reagents and conditions: (a) i—(2R)-methyl glycidate, LiOTf, *t*-BuOH, 70 °C; ii—CDI, CH₂Cl₂, rt, 20–59% for two steps; (b) for 4a–d, NH₃, MeOH, rt; for 4e–h, MeNH₂, MeOH, rt; 35–39%.

The desired carboxamides **4a**-**h** were then synthesized by reacting the methyl esters **11a**-**d** with either ammonia or methyl amine.

The homomorpholine oxazolidinone analogs **2–4** were tested against a panel of Gram-positive bacteria. Minimum inhibitory concentration (MIC, in μ g/mL) values were determined by micro broth methodology.⁹ The *Escherichia coli* in vitro transcription and translation (TnT) assay was performed in 96-well microtiter plates using a luciferase reporter system.¹⁰ The effects of fluorine substitution on the phenyl ring (B-ring) as well as the effects of various C-5 substitution on the antibacterial activities are shown in Table 1. MIC data for linezolid **1** are provided for comparison.

Homomorpholine C-5 acetamide analogs with mono-, di-, and tri-fluoro phenyl B-rings (2b-d) were roughly equipotent in vitro as linezolid 1. On the whole, the diffuorophenyl analogs were shown to be more potent in vitro compared to desfluoro, monofluoro, and trifluorophenyl analogs, with desfluoro analogs generally being least potent. The in vitro antibacterial activity of C-5 carboxamide analogs (4a-h) was disappointing as these compounds were all less potent than linezolid. However, it has been demonstrated with several difluorophenyl-oxazolidinone analogs that analogs with various C-5 functionalities such as methyl carbamate 2n, ethyl amide **20**, triazolo analog **3b**, and ethynyl triazolo analog 3d resulted in in vitro antibacterial activity comparable to linezolid. Overall, novel homomorpholine oxazolidinones, in which linezolid's morpholine C-ring was replaced with the larger homomorpholine ring, have

Table 1.	Minimum	inhibitory	concentrations	(MICs,	$\mu g/mL)$ for	compounds	1, 2a-g	, 2 j,	2m-r, 3	a-d,	4a-h

Compound	Х	Y	Ζ	R	EC TnT IC ₅₀ (μ M)	S. a. MIC	S. p. MIC	S. py. MIC	E. f. MIC
1 linezolid					3.6	2	1	2	4
2a	Н	Н	Н	_		8	8	8	16
2b	F	Н	Н	_	2.30	4	2	2	2
2c	F	F	Н	_	1.67	2	1	1	1
2d	F	F	F	_	3.93	2	1	2	2
2e	Н	Н	Н			16	16	32	32
2f	F	Н	Н	_		32	32	32	64
2g	F	F	Н			8	16	8	32
2j	F	Н	Н	_		>64	>64	>64	>64
2m	Н	Н	Н	NHC(=O)OMe		16	16	8	16
2n	F	F	Н	NHC(=O)OMe	1.90	2	1	1	2
20	F	F	Н	NHC(=O)Et	2.10	2	2	1	2
2p	F	F	F	NHC(=O)Et	3.49	4	4	4	4
2q	Н	Н	Н	_ `		>64	>64	>64	>64
2r	F	F	Н			4	4	2	8
3a	Н	Н	Н	_		16	16	8	32
3b	F	F	Н	_		2	2	1	2
3c	F	F	Н	_		>32	4	2	>32
3d	F	F	Н	_		4	2	2	2
4a	Н	Н	Н	Н		32	32	64	64
4b	F	Н	Н	Н		8	16	8	16
4c	F	F	Н	Н	5.87	4	4	4	8
4d	F	F	F	Н	23.4	16	16	16	32
4e	Н	Н	Н	Me		32	32	32	64
4f	F	Н	Н	Me		16	8	8	16
4g	F	F	Н	Me	6.37	4	4	4	8
4h	F	F	F	Me	18.9	16	16	16	32

Strains: S. a., Staphylococcus aureus UC-76 SA-1; S. p., Streptococcus pneumoniae SV1 SP-3; E. f., Enterococcus faecalis MGH-2 EF1-1; S. py., Streptococcus pyogenes C-203.

shown to retain antibacterial potency with in vitro activity of many compounds synthesized in this series comparable to linezolid's in vitro activity.

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