Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 19 (2009) 550–553
Bioorganic & Medicinal Chemistry Letters

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

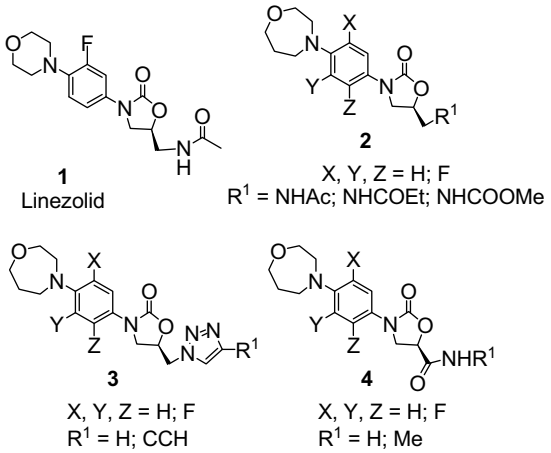
Ji-Young Kim,* Frederick E. Boyer, Allison L. Choy, Michael D. Huband, Paul J. Pagano and J. V. N. Vara Prasad

Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

Received 6 December 2007; revised 15 February 2008; accepted 21 February 2008
Available online 26 February 2008

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.

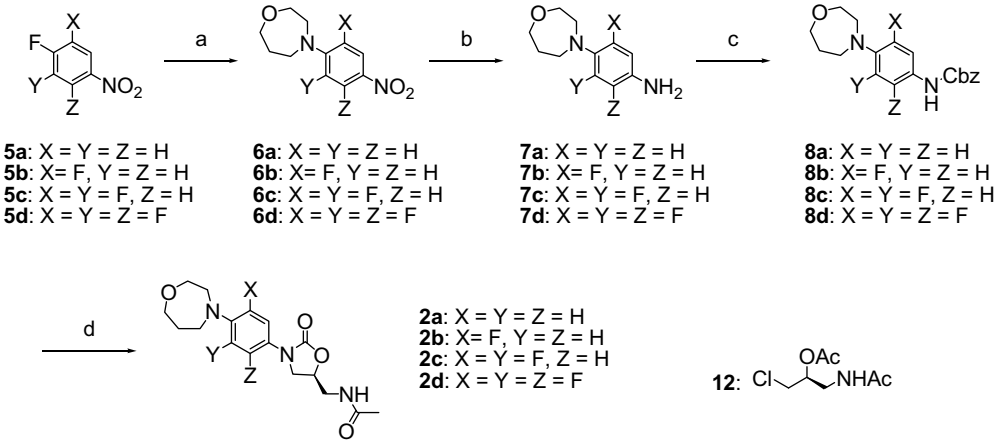
Oxazolidinones are a new class of totally synthetic antibiotics with activity against Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).[1] Linezolid (Zyvox™) **1** is the first drug of this class to be approved for the treatment 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, 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**), 3,4,5-tri-fluorobenzene (**5c**), and 3,4,5,6-tetrafluoronitroben-

Keywords: Oxazolidinone; Antibacterial agents; Homomorpholine; Gram-positive; Linezolid; Synthesis of analogs; Structure–activity relations.
* Corresponding author. Tel.: +1 860 686 9320; fax: +1 860 686 0590; e-mail: ji-young.kim@pfizer.com

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.02.052



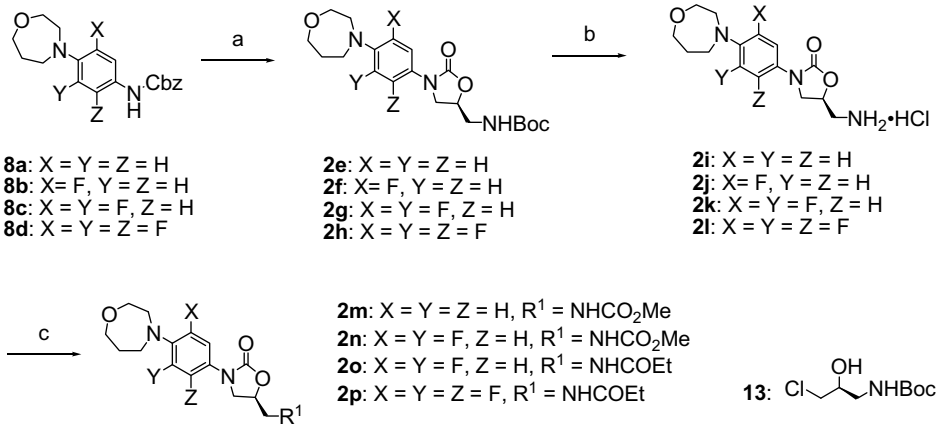
Scheme 1. Reagents and conditions: (a) homomorpholine hydrochloride, $(i\text{-Pr})_2NEt$; for **5a**, NMP, 50 °C; for **5b** and **5d**, NMP, −20 °C; for **5c**, CH_3CN, 0 °C; 88–100%; (b) Raney Ni, H_2, THF, 50 psi, 95–100%; (c) CbzCl, pyr, CH_2Cl_2, rt, 70–100%; (d) (2*S*)-3-acetamido-1-chloropropan-2-yl 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 (2*S*)-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**).

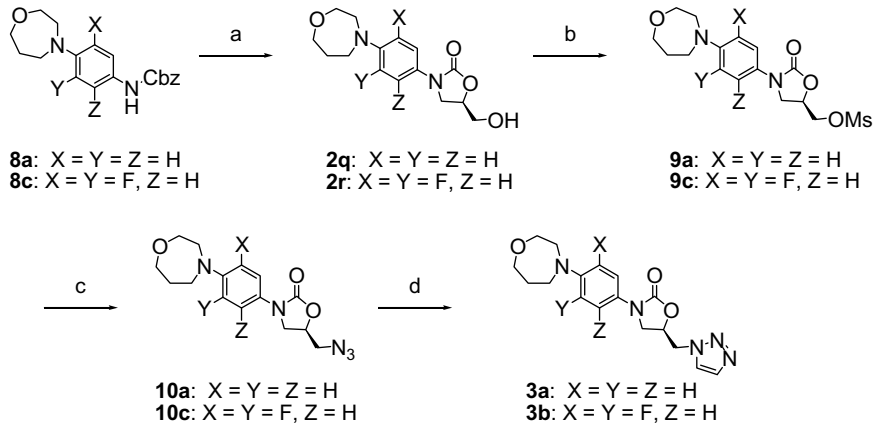
The preparation of the C-5 ethyl amides (**2o**,**p**) and the C-5 carbamate analogs (**2m**,**n**) was achieved by first forming the *tert*-butyl carbamate intermediates **2e**–**h** by reacting the benzyl carbamates **8a**–**d** with (2*S*)-*tert*-butyl 3-chloro-2-hydroxypropyl carbamate **13** and 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 **2o**,**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 (2*R*)-glycidyl butyrate and *n*-butyllithium. This step led to the closure of the oxazolidinone ring and cleavage of the resulting butyric ester in one-pot 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-2,5-diene to provide the desired oxazolidinones with C-5 triazole **3a**,**b**.

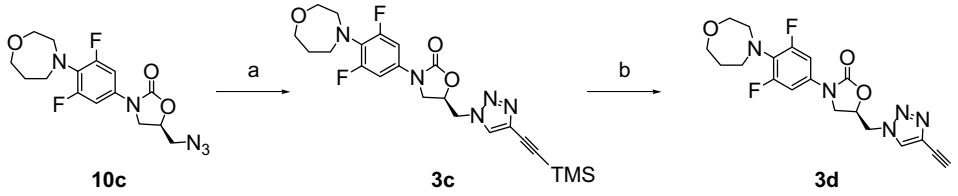
The conversion of C-5-azidomethyl-3,5-difluorophenyl-oxazolidinone **10c** to the corresponding ethynyltriazolo-3,5-difluorophenyl-oxazolidinone **3d** was carried out utilizing a regioselective Cu(I) catalyzed cycloaddition as illustrated in Scheme 4.[8] The transformation of azide **10c** to the trimethylsilyl 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**, $NaHCO_3$, methyl chloroformate, THF/H_2O, rt; for **2o**,**p**, $NaHCO_3$, propionic anhydride, THF/H_2O, rt; 85–95%.



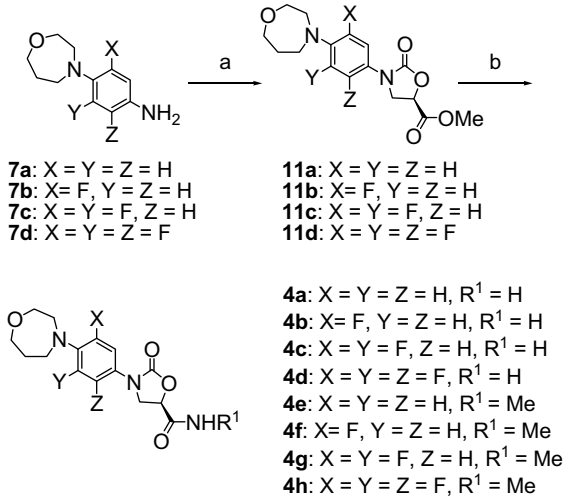
Scheme 3. Reagents and conditions: (a) (2*R*)-glycidyl butyrate, *n*-BuLi, THF, −78 °C, 47–82%; (b) NEt_3, MsCl, CH_2Cl_2, 0 °C, 100%; (c) NaN_3, DMF, 75 °C, 84–100%; (d) bicyclo[2.2.1]hepta-2,5-diene, dioxane, 101 °C (reflux), 18–47%.



Scheme 4. Reagents and conditions: (a) TMS-1,3-butadiyne, 2,6-lutidine, CuI, CH_3CN, 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 ethynyl 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 (2*R*)-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—(2*R*)-methyl glycidate, LiOTf, *t*-BuOH, 70 °C; ii—CDI, CH_2Cl_2, rt, 20–59% for two steps; (b) for **4a**–**d**, NH_3, MeOH, rt; for **4e**–**h**, $MeNH_2$, 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 μg/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 difluorophenyl 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 **2o**, 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, μg/mL) for compounds **1**, **2a–g**, **2j**, **2m–r**, **3a–d**, **4a–h**

Compound	X	Y	Z	R	EC TnT IC_{50} (μM)	S. a. MIC	S. p. MIC	S. py. MIC	E. f. MIC
1 linezolid					3.6	2	1	2	4
2a	H	H	H	—		8	8	8	16
2b	F	H	H	—	2.30	4	2	2	2
2c	F	F	H	—	1.67	2	1	1	1
2d	F	F	F	—	3.93	2	1	2	2
2e	H	H	H	—		16	16	32	32
2f	F	H	H	—		32	32	32	64
2g	F	F	H	—		8	16	8	32
2j	F	H	H	—		>64	>64	>64	>64
2m	H	H	H	NHC(=O)OMe		16	16	8	16
2n	F	F	H	NHC(=O)OMe	1.90	2	1	1	2
2o	F	F	H	NHC(=O)Et	2.10	2	2	1	2
2p	F	F	F	NHC(=O)Et	3.49	4	4	4	4
2q	H	H	H	—		>64	>64	>64	>64
2r	F	F	H	—		4	4	2	8
3a	H	H	H	—		16	16	8	32
3b	F	F	H	—		2	2	1	2
3c	F	F	H	—		>32	4	2	>32
3d	F	F	H	—		4	2	2	2
4a	H	H	H	H		32	32	64	64
4b	F	H	H	H		8	16	8	16
4c	F	F	H	H	5.87	4	4	4	8
4d	F	F	F	H	23.4	16	16	16	32
4e	H	H	H	Me		32	32	32	64
4f	F	H	H	Me		16	8	8	16
4g	F	F	H	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.

References and notes

1. For recent reviews of linezolid, see: (a) Wilcox, M. H. *Expert Opin. Pharmacother.* **2005**, *6*, 2315; (b) Stevens, D. L.; Madaras-Kelly, K. *Expert Rev. Anti Infect. Ther.* **2004**, *2*, 51; (c) Nilius, A. M. *Curr. Opin. Investig. Drugs* **2003**, *4*, 149; (d) Moellering, R. C. *Ann. Inter. Med.* **2003**, *138*, 135.
2. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
3. Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010.
4. Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, 499.
5. Poel, T.-J.; Thomas, R. C.; Adams, W. J.; Aristoff, P. A.; Barbachyn, M. R.; Blakeman, D. P.; Boyer, F. E.; Brieland, J.; Brideau, R.; Brodfuehrer, J.; Choy, A. L.; Dority, M.; Ford, C. W.; Gadwood, R. C.; Hamel, J. C.; Huband, M. D.; Huber, C.; Kim, J.-Y.; Joseph, M.; Pagano, P. J.; Ross, D.; Zhu, T.; Zurenko, G. E.; Vara Prasad, J. V. N. *J. Med. Chem.* **2007**, *50*, 5886.
6. (a) For experimental details and ^{1}H NMR data, see: Vara Prasad, J. V. N.; Boyer, F. E.; Kim, J.-Y. WO 2007/000644 A; (b) Barbachyn, M. R.; Brickner, S. J. WO 95/07271 A; (c) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jegan-Herrnton, P. M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T. *Org. Process Res. Dev.* **2003**, *7*, 533.
7. The nucleophilic aromatic substitution resulted only in the desired regioisomers in high yields with no other regioisomers detected during the reaction. Highly regioselective reactions of this type, indicated by extreme high yields of the desired isomers, have been previously reported: Barbachyn, M. R.; Harris, C. R.; Vara Prasad, J. V. N. WO 2005/113520 A1.
8. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
9. Clinical and Laboratory Standards Institute (formerly, National Committee for Clinical Laboratory Standards). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria*; Approved Standard, 6th ed.; NCCLS Document M11-A6; Vol. 24, No. 2.
10. (a) Murray, R. W.; Melchior, E. P.; Hagadorn, J. C.; Marotti, K. R. *Antimicrob. Agents Chemother.* **2001**, *45*, 1900; (b) Zubay, G. *Ann. Rev. Genet.* **1973**, *7*, 267.