Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 857–859

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Antibacterial Activity of Linezolid Analogues

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Received 2 November 2001; accepted 28 December 2001

Abstract—Several new compounds of oxazolidinone class were designed and synthesized referring to the structure–activity relationship studies and the synthesis of Linezolid, and their antibacterial activity was studied.

Introduction

The increasing incidence of multidrug resistance among Gram-positive bacterial pathogens represents one of the major challenges in the 1990s for health care researchers. This growing problem has recently rekindled interest in the search for new antibiotic structural classes that inhibit or kill by novel mechanisms. Clearly there is an urgent need for the discovery and development of new agents effective against the emerging and currently problematic Gram-positive pathogens MRSA, methicillin-resistant coagulase-negative *staphylococci*, VRE, and penicillin-resistant *pneumococci*, as well as the perceived looming threat of a vancomycin-resistant *Staphylococcus aureus*.

The oxazolidinones are a new class of totally synthetic antibacterial agents. They have a novel mechanism of action that involves the inhibition of bacterial protein synthesis at a very early stage, prior to chain initiation.[1]

Linezolid (U-100766) is a successful agent of this class, and has already gained the permission of the FDA and come into the market.

Referring to the structure–activity relationship studies[3–7] and the synthesis of Linezolid,[2] we have designed some new compounds of oxazolidinone class in order to investigate the relationship of antibacterial activity and the increasing lipophilicity of group R (Fig. 1). These compounds all belong to piperazinyl series. Figure 1 shows several compounds already synthesized (**1a**–**d**) and we also prepared some U-100766 for contrast (Fig. 1, **1e**).

Chemistry

The synthesis route of these compounds is shown in Figure 1. Commencing with 3,4-difluoronitrobenzene, nucleophilic aromatic displacement with excess substituted piperazine (RH) selectively gave the *p*-substituted nitrobenzene (**2**). Reduction of **2** was followed by attachment of benzyl chloroformate activating group to the arylamine **3** giving **4**. Carbamate **4** was deprotonated with *n*-BuLi (THF, −78 °C), and then (*R*)-glycidyl butyrate was added and the mixture was kept at −78 °C for about 1.5 h, then slowly allowed to warm to room temperature and stirred overnight. This sequence provided directly the (5*R*)-(hydroxy methyl)-2-oxazolidinone **5** in >55% yield. **5** was reacted with 4-nitrobenzenesulfonyl chloride and gave **6**. **6** then reacted with NH_3 in methyl alcohol, and gave **7**. **7** was not purified but just handled with water, solution of citric acid and CH_2Cl_2. Then the mixture (made pH > 8.5) was reacted with acetic anhydride at 40 °C for 2 h, and gave **1.**

In total, we have synthesized four target compounds and 16 intermediates; all of them are not reported yet. The structures of all the target compounds were proved by ^{1}H NMR, MS and HRMS (data shown in Table 1 and ref 8).

Biological Results and Discussion

Using U-100766 and Norvancomycin as control, we tested the antibacterial activity in vitro of the target

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0960-894X/02/$ - see front matter
PII: S0960-894X(02)00043-4

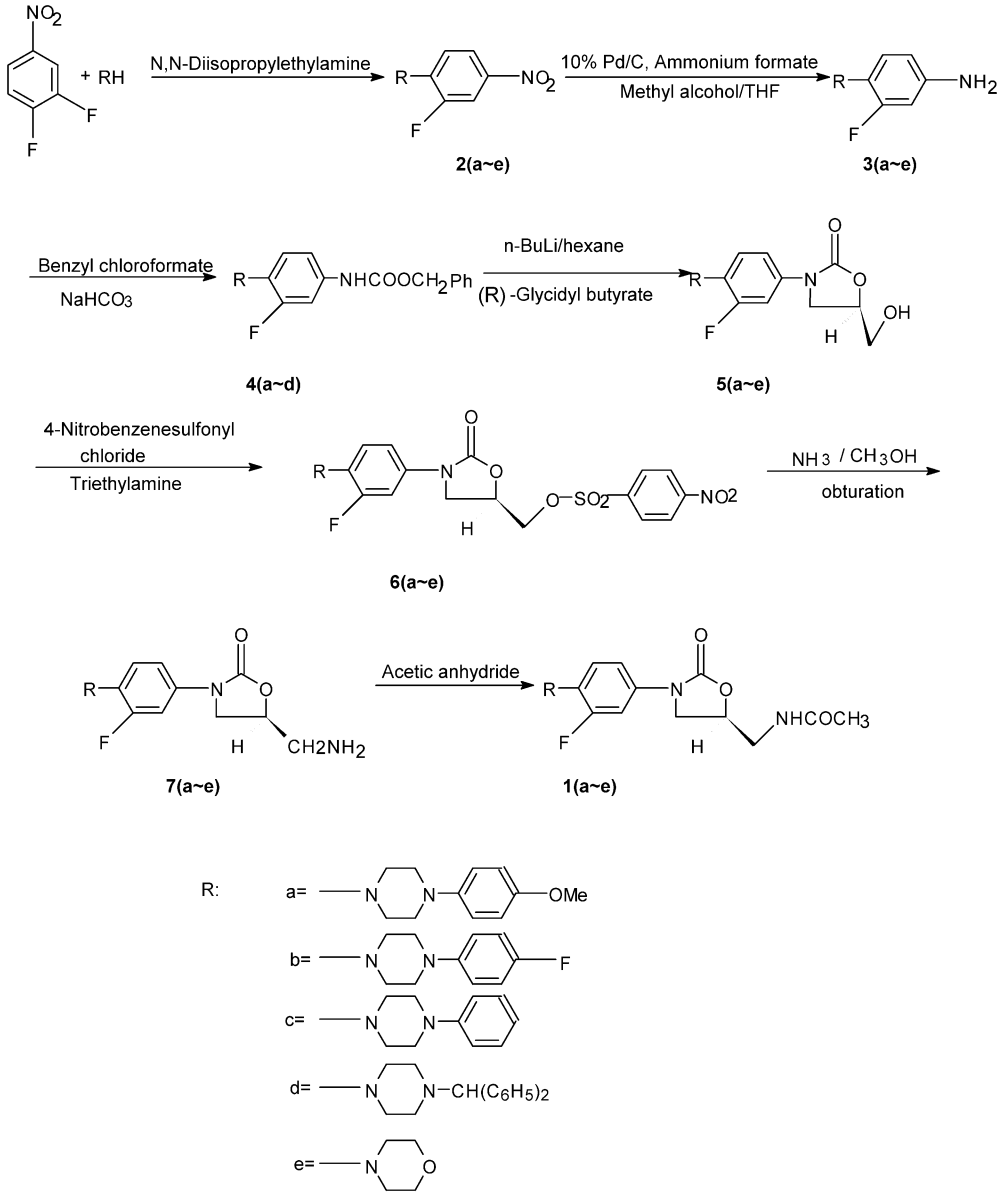

Figure 1. Synthesis route.

Table 1. ^{1}H NMR, MS and HRMS data of target compounds

	Compound data
1a	^{1}H NMR($CDCl_3$) δ (ppm): 2.03 (3H, s, $-COCH_3$), 3.20–3.34 (8H, m, piperizine), 3.78 (3H, s, –OMe), 3.58–4.06 (4H, m, 2× $-CH_2-$), 4.75–4.78 (1H, m, –CH–), 5.96 (1H, br, –NH–), 6.87–7.10 (6H, m, ArH), 7.45–7.50 (1H, m, ArH); MS-EI (*m*/*z*): 442 (M^+), 398 (M^+-CO_2), 135 ($C_8H_9N_1O_1$); HRMS $C_{23}H_{27}N_4O_4F$, calc. (M): 442.201634; meas.: 442.201948
1b	^{1}H NMR ($CDCl_3$) δ (ppm): 2.03 (3H, s, $-COCH_3$), 3.24–3.27 (8H, m, piperizine), 3.61–4.06 (4H, m, 2×$-CH_2-$), 4.72–4.80 (1H, m, –CH–), 6.00 (1H, br, –NH–), 6.95–7.11 (6H, m, ArH), 7.44–7.48 (1H, m, ArH); MS-EI (*m*/*z*): 430 (M^+), 386 (M^+-CO_2), 150 ($C_9H_9N_1F_1$), 123 ($C_7H_6N_1F_1$); HRMS $C_{22}H_{24}N_4O_3F_2$, calc. (M): 430.181647; meas.: 430.182161
1c	^{1}H NMR ($CDCl_3$) δ (ppm): 2.05 (3H, s, $-COCH_3$), 3.25–3.39 (8H, m, piperizine), 3.56–4.06 (4H, m, 2× $-CH_2-$), 4.75–4.79 (1H, m, –CH–), 5.99 (1H, br, –NH–), 6.96–7.10 (5H, m, ArH), 7.30–7.50 (3H, m, ArH); MS-EI (*m*/*z*): 412 (M^+), 368 (M^+-CO_2), 105 (C_7H_7N); HRMS $C_{22}H_{25}N_4O_3F$, calc. (M): 412.191069; meas.: 412.193418
1d	^{1}H NMR ($CDCl_3$) δ (ppm): 2.02 (3H, s, $-COCH_3$), 2.47–2.67 (4H, m, piperizine), 2.98–3.10 (4H, m, piperizine), 3.53–4.03 (4H, m, 2× $-CH_2-$), 4.29 (1H, s, –CH–), 4.71–4.79 (1H, m, –CH–), 5.97 (1H, br, –NH–), 6.89–7.45 (13H, m, ArH); MS-EI (*m*/*z*): 502 (M^+), 459 (MH^+-CO_2), 336 (MH^+-ph_2CH), 195 ($C_{14}H_{13}N_1$), 167 (ph_2CH); HRMS $C_{29}H_{31}N_4O_3F$, calc.(M): 502.238019; meas.: 502.236347
1e	^{1}H NMR($CDCl_3$) δ (ppm): 2.02 (3H, s, $-COCH_3$), 3.04–3.07 (4H, m, $(CH_2)_2N$), 3.86–3.88 (4H, m, $(CH_2)_2O$), 3.59–4.05 (4H, m, 2× $-CH_2-$), 4.73–4.81 (1H, m, –CH–), 6.34 (1H, br, –NH–), 6.94 (1H, t, $J=9.0$ Hz, ArH), 7.04–7.08 (1H, dd, $J_1=2.1$ Hz, $J_2=8.8$ Hz, ArH), 7.41–7.46 (1H, dd, $J_1=3.0$ Hz, $J_2=14.7$ Hz, ArH); MS-EI (*m*/*z*): 337 (M^+), 293 (M^+-CO_2), 234 ($C_{13}H_{15}N_2OF$); HRMS $C_{16}H_{20}N_3O_4F$, calc. (M): 337.143785; meas. 337.144878

Table 2. Antibacterial activity

Strain	MIC (μg/mL)					
	1e Linezolid	**1a**	**1b**	**1c**	**1d**	Norvancomycin
S. pneumoniae 9753	0.5	1	1	0.5	4	0.25
S. pneumoniae 9757	0.5	1	1	0.25	4	0.25
S. pneumoniae 9798	0.5	1	1	1	8	0.25
Streptococcus A 29	0.25	1	1	0.5	4	0.5
Streptococcus A 44	0.5	1	1	2	32	0.5
S. pyogenes 102	0.5	1	1	1	32	0.5
S. pyogenes 114	0.5	2	2	1	16	2
E. faecalis 50	0.5	1	1	1	8	1
E. faecalis 68	1	2	4	2	32	2
S. aureus 975	0.25	1	0.5	1	4	1
S. aureus 9616	1	1	2	1	8	0.5
S. aureus 9721	0.5	1	1	1	16	1
S. aureus 9776	0.5	1	1	1	8	1
S. aureus 966	0.5	2	1	2	8	2
S. epidermidis 975	0.5	1	1	1	8	1
S. epidermidis 9753	0.25	1	0.5	0.5	4	1
S. epidermidis 9759	0.5	1	1	1	16	1

compounds with several clinical separated pathogens, several quality control strains and several standard strains. The target compounds **1a**–**d** were dissolved in DMSO and we tested MICs with double dilution method. The results are shown in Table 2. The activity of **1d** is very poor. The activity of the other three compounds is equal to or less than U-100766 and Norvancomycin. Because we only get a certain number of compounds, we cannot discuss the SAR in depth now. Here, we just report the synthesis and antibacterial activity of these analogues and more analogues will be prepared for this purpose soon.

Acknowledgements

The authors would like to thank the National Research Center of Drug and Metabolite Analysis for measuring the data of ^{1}H NMR, MS and HRMS, and we also want to thank the Pharmacology Laboratory of Institute of Medicinal Biotechnology for testing the antibacterial activity.

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8. Physical constants: **1a**: mp: 226–230 °C; $[\alpha]_D^{27}$ (°): −6 (*c* 0.63, DMSO). **1b**: mp: 222–226 °C; $[\alpha]_D^{27}$ (°): −2.7 (*c* 0.76, $CHCl_3$). **1c**: mp: 206–209 °C; $[\alpha]_D^{27}$ (°): −12 (*c* 2.03, $CHCl_3$). **1d**: $[\alpha]_D^{27}$ (°): −7 (*c* 5.52, $CHCl_3$). **1e**: mp: 181–183 °C; $[\alpha]_D^{27}$ (°): −11 (*c* 5.10, $CHCl_3$).