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Synthesis and antibacterial activity of some aryloxy/thioaryloxy oxazolidinone derivatives

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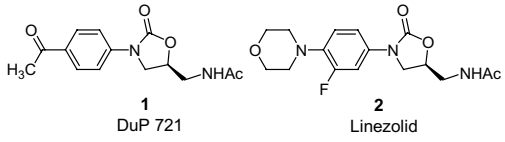
Abstract—A series of aryloxy/thioaryloxy oxazolidinone derivatives has been synthesized and tested for in vitro antibacterial activity by MIC determination against a panel of susceptible and resistant Gram-positive and Gram-negative microorganisms, some of which are resistant to methicillin and vancomycin. Compounds **12a**, **12b**, **14a**, and **14b** from this series were found to be equipotent or more potent than linezolid in vitro.

The oxazolidinones, a new class of synthetic antimicrobial agents, are active against numerous multi-drug-resistant Gram-positive organisms.[1] Particularly, problematic pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. Their mode of action has been found to inhibit protein synthesis in the initial stage.[2] Due to this novel mechanism of action, oxazolidinones are not cross resistant with other types of antibiotics. This class was discovered through broad screening and is exemplified by the erstwhile clinical candi- date DuP 721 (**1**, Fig. 1).[3–5]

Early studies of DuP 721 revealed a number of attractive features but despite these attractive features, the development of DuP 721 was terminated.[6] Pharmacia group found Linezolid (**2**, Fig. 1),[7,8] which is well known as the first promising candidate of oxazolidinone and works effectively against numerous serious Gram-positive human pathogens caused by MRSA and VRE.



1 DuP 721 **2** Linezolid

Figure 1.

The potential of this new antibacterial class has stimulated an exploratory chemical analog program in our discovery research laboratories. In the present communication, we wish to report the synthesis and microbiological evaluation of a series of hitherto unknown substituted aryloxy/thioaryloxy oxazolidinone derivatives **12**, **14**–**18**.

Compounds **12**, **14**–**18** were synthesized in various steps as shown in Scheme 1. Compound **7** was synthesized starting from 1,2-difluoro-4-nitrobenzene (**3**). Compound **3** on condensation with 4-acetamidophenol/thiophenol in the presence of K_2CO_3 in DMF at 80 °C gave *N*-(4-[2-fluoro-4-nitro-phenoxy/phenylthio]phenyl)acetamide (**5**) in excellent yields, which on reduction by Pd–C/H_2 followed by condensation with benzyl chloroformate gave benzyl 4-(4-[acetylamino]phenoxy/phenylthio)-3-fluorophenyl-carbamate (**7**). Conversion

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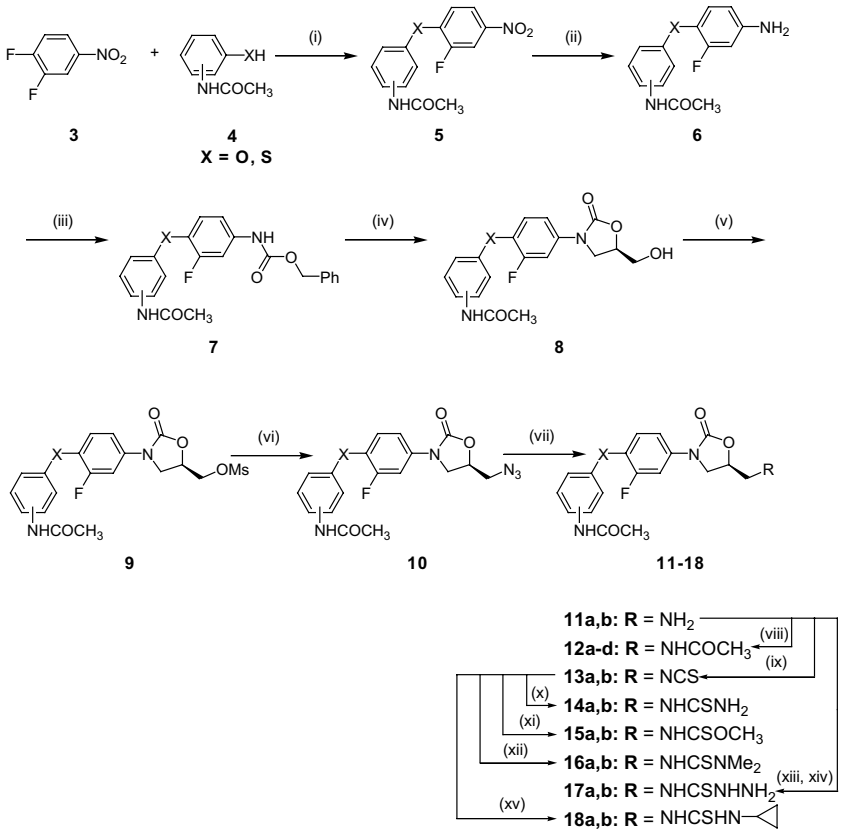

Scheme 1. Reagents and conditions: (i) K_2CO_3, DMF, 75–80 °C, 3–4 h; (ii) 10% Pd–C, HCO_2NH_4, MeOH, reflux, 0.5–1 h; (iii) Cbz-Cl, Na_2CO_3, acetone–H_2O (2:1), 0 → 25 °C, 3 h; (iv) *n*-BuLi, (*R*)-glycidyl butyrate, THF, −78 → 25 °C, 12 h; (v) MsCl, TEA, DCM, 0–25 °C, 3–4 h; (vi) NaN_3, DMF, 80 °C, 5–6 h; (vii) PPh_3, acetonitrile, 45 °C, 1 h, H_2O, 65–70 °C, 3–4 h; (viii) Ac_2O, pyridine, 25 °C, 3–4 h; (ix) CS_2 solution, $ClCO_2Et$, TEA, THF, 0 → 25 °C, 12–14 h; (x) MeOH–NH_3, 0–5 °C, 4–6 h; (xi) NaH, MeOH, 0–5 °C, 2–3 h; (xii) $Me_2NH{\cdot}HCl$, TEA, DCM, 0 → 25 °C, 2–3 h; (xiii) phenyl chlorothionoformate, pyridine, PhH, 25 °C, 2–4 h; (xiv) $NH_2NH_2{\cdot}H_2O$, dioxane, reflux, 0.5–1 h; (xv) cyclopropylamine, DCM, 0 → 25 °C, 4–5 h.

of compound **7** to *N*-(4-{2-fluoro-4-[(5*R*)-5-(hydroxymethyl)-2-oxo-1,3-oxazolidin-3-yl]phenoxy/phenylthio}-phenyl)acetamide (**8**) was accomplished by use of *n*-butyl lithium and (*R*)-glycidyl butyrate in THF at −78 °C. The alcohol **8** was reacted with methanesulfonyl chloride, followed by treatment with sodium azide to yield *N*-(4-{4-[(5*S*)-5-(azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]-2-fluoro-phenoxy/phenylthio}phenyl)acetamide (**10**). Reduction of azide **10** using PPh_3 gave the key intermediate *N*-(4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-2-fluoro-phenoxy/phenylthio}phenyl)-acetamide (**11a** and **11b**). Acetylation of **11** with acetic anhydride in pyridine gave *N*-(4-{4-[(5*S*)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluoro-phenoxy/phenylthio}phenyl)acetamide (**12a** and **12b**) in quantitative yields. Thiourea derivatives **14a** and **14b** were obtained from the isothiocyanate **13a** and **13b**, which were easily derived from key intermediate **11** by treatment with carbon disulfide solution and ethyl chloroformate. The thiocarbamate derivatives **15a** and **15b** were prepared from **13a** and **13b** by treatment with NaH and methanol. Compounds **16**–**17a** and **16**–**17b** were prepared by reacting isothiocyanate **13** with dimethylamine and cyclopropylamine, respectively. Compounds **18a** and **18b** were also prepared by the condensation of **11** with phenyl chlorothionoformate followed by its reaction with hydrazine hydrate in dioxane (Scheme 1). All new compounds reported here were fully characterized on the basis of complementary spectroscopic (^{1}H NMR and MS) and analytical data.[9]

A large number of compounds were synthesized (Table 1) and evaluated for antibacterial activity by agar diffusion and agar dilution method as per NCCLS recommendations.[10] Among them, 12 compounds exhibited mild to good activity in the preliminary screen (agar diffusion assay) at 50 and 25 μg concentrations. All these compounds were then tested for determination of minimal inhibitory concentration (MIC) against a panel of Gram-positive and Gram-negative organisms, some of which are resistant to methicillin and vancomycin. Their MIC (μg/mL) are shown in Table 1. Linezolid was used as reference compound.

The antibacterial data in Table 1 clearly show that compounds **12a** and **14a** containing *p*-acetamido phenol are nearly as active as linezolid in vitro MIC assay against sensitive and drug resistant gram-positive bacteria though both the compounds have different substitution at the other end of oxazolidinone ring (**12a**: R = $NHCOCH_3$, **14a**: R = $NHCSNH_2$). Further, the replacement of phenol by thiophenol (**12b** and **14b**) led to increase in antibacterial activity. This suggests that the thiophenol moiety is more preferable as compared to phenol.

Table 1. MIC values (μg/mL) of new oxazolidinones **12a–d**, **14–18a,b** in several Gram-positive and Gram-negative bacteria

Compds	$NHCOCH_3$	R	X	S.a.	MRSA	S.e.	MRSE	E.f. I	E.f. II	E.f. III	E.d.	B.c.	E.c.	P.a.	K.p.	S.m.	S.a.	S.t.
12a	*p*-$NHCOCH_3$	$NHCOCH_3$	O	2	2–4	2	4	4	4	4	4	>16	>16	>16	>16	>16	>16	>16
12b	*p*-$NHCOCH_3$	$NHCOCH_3$	S	1	1–2	1	2	2	2	2	2	>16	>16	>16	>16	>16	>16	>16
12c	*o*-$NHCOCH_3$	$NHCOCH_3$	O	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
12d	*m*-$NHCOCH_3$	$NHCOCH_3$	O	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
14a	*p*-$NHCOCH_3$	$NHCSNH_2$	O	2	2–4	2	4	4	4	4	2	>16	>16	>16	>16	>16	>16	>16
14b	*p*-$NHCOCH_3$	$NHCSNH_2$	S	1	1–2	1	2	2	2	2	2	>16	>16	>16	>16	>16	>16	>16
15a	*p*-$NHCOCH_3$	$NHCSOCH_3$	O	8	16->16	8	16	8	8	16	8	>16	>16	>16	>16	>16	>16	>16
15b	*p*-$NHCOCH_3$	$NHCSOCH_3$	S	4–8	4–8	4	8	4	8	4	4	>16	>16	>16	>16	>16	>16	>16
16a	*p*-$NHCOCH_3$	$NHCSNMe_2$	O	16	16->16	16	16	16	16	>16	16	>16	>16	>16	>16	>16	>16	>16
16b	*p*-$NHCOCH_3$	$NHCSNMe_2$	S	16	>16	16	16	8	16	>16	16	>16	>16	>16	>16	>16	>16	>16
17a	*p*-$NHCOCH_3$	$NHCSNHNH_2$	O	4	4–16	4	8	4	8	4	4	>16	>16	>16	>16	>16	>16	>16
17b	*p*-$NHCOCH_3$	$NHCSNHNH_2$	S	4	4–8	4	4	4	8	16	8	>16	>16	>16	>16	>16	>16	>16
18a	*p*-$NHCOCH_3$		O	>16	16->16	16	16	8	16	>16	16	>16	>16	>16	>16	>16	>16	>16
18b	*p*-$NHCOCH_3$		S	16	16->16	8	8	8	>16	8	8	>16	>16	>16	>16	>16	>16	>16
Linezolid	—	—	—	2	2	2	2	2	2	2	2	>16	>16	>16	>16	>16	>16	>16

S.a. = *Staphylococcus aureus* ATCC 25923 and 29213; MRSA = methicillin resistant *Staphylococcus aureus* ST450, ATCC 15187, ICH 1 and 37; S.e. = *Staphylococcus epidermidis* ATCC 12228; MRSE = methicillin resistant *Staphylococcus epidermidis* ATCC 23760; E.f. I = *Enterococcus faecalis* ATCC 29212 and 21777; E.f. II = *Enterococcus faecalis* (VRE) ATCC 346-VRE & 5B-VRE; E.f. III = *Enterococcus faecium* 6A-VRE; E.d. = *Enterococcus durans* ATCC 581; B.c. = *Bacillus cereus* ; E.c. = *Escherichia coli* ATCC 25922; P.a. = *Pseudomonas aeruginosa* ATCC 27853; K.p. = *Klebsiella pneumoniae* ATCC 15380; S.m. = *Serratia marcescens* ATCC 12999; S.a. = *Salmonella abony* NCTC 6017; S.t. = *Salmonella typhi* (MDR) ICH 098.

Further, we also modified the thiourea group into thiocarbamate (**15a** and **15b**) and found a decrease in antibacterial activity, however, **15b** is found to be slightly superior to its phenolic analog **15a**. The data given in Table 1 reveal that any bulky substituent (**16**–**18a**,**b**) led to the significant loss in antibacterial activities, which suggests that bulky substituents are not favorable.

It is worth mentioning that compounds **12b** and **14b** containing *p*-acetamido thiophenol group showed comparable antibacterial activity against MRSA and VRE with that of linezolid.

In summary, a number of aryloxy/thioaryloxy oxazolidinone derivatives were synthesized and evaluated for microbiological activity against resistant and susceptible Gram-positive organisms were found to have activity comparable to linezolid. These findings clearly indicate that small groups are well tolerated on the methylamino moiety of oxazolidinone ring; however, bulky substituent at this end resulted in loss of activity.

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9. Analytical data for compounds **12**, **14–18**. ^{1}H NMR spectra were recorded on Bruker Advance DRX 200 MHz instrument as solutions in $CDCl_3$ otherwise mentioned. **12a**: ^{1}H NMR: δ 7.85 (br s, 1H), 7.80 (br s, 1H), 7.60–7.65 (m, 2H), 6.95–7.00 (m, 1H), 6.80–6.85 (m, 2H), 6.50–6.60 (m, 1H), 6.30–6.35 (m, 1H), 3.95–4.50 (m, 3H), 3.40–3.65 (m, 2H), 2.00 (s, 3H), 1.75 (s, 3H). MS: *m/z* 402 (M+1). Anal. Calcd for $C_{20}H_{20}FN_3O_5$: C, 59.85; H, 5.02; N, 10.47. Found: C, 59.54; H, 4.83; N, 10.25. **12b**: ^{1}H NMR: δ 7.85–7.90 (m, 3H), 7.75 (br s, 1H), 7.20–7.25 (m, 1H), 7.10–7.15 (m, 2H), 6.45–6.75 (m, 2H), 3.95–4.25 (m, 3H), 3.45–3.65 (m, 2H), 2.05 (s, 3H), 1.75 (s, 3H). MS: *m/z* 418 (M+1). Anal. Calcd for $C_{20}H_{20}FN_3O_4S$: C, 57.54; H, 4.83; N, 10.07. Found: C, 57.69; H, 4.99; N, 10.32. **12c**: ^{1}H NMR: δ 12.00 (br s, 1H), 7.40–7.45 (m, 1H), 7.10–7.20 (m, 2H), 6.65–6.85 (m, 2H), 6.25–6.35 (m, 2H), 5.85–5.95 (br s, 1H), 3.95–4.20 (m, 3H), 3.40–3.70 (m, 2H), 2.10 (s, 3H), 1.85 (s, 3H). MS: *m/z* 402 (M+1). Anal. Calcd for $C_{20}H_{20}FN_3O_5$: C, 59.85; H, 5.02; N, 10.47. Found: C, 60.07; H, 5.24; N, 10.71. **12d**: ^{1}H NMR: δ 9.35 (br s, 1H), 7.00–7.20 (m, 3H), 6.90–6.95 (m, 1H), 6.70–6.65 (m, 1H), 6.55–6.50 (m, 1H), 6.30–6.35 (m, 1H), 5.80–5.90 (br s, 1H), 3.90–4.25 (m, 3H), 3.45–3.65 (m, 2H), 2.15 (s, 3H), 1.90 (s, 3H). MS: *m/z* 402 (M+1). Anal. Calcd for $C_{20}H_{20}FN_3O_5$: C, 59.85; H, 5.02; N, 10.47. Found: C, 59.99; H, 5.33; N, 10.62. **14a**: ^{1}H NMR: δ 9.95 (br s, 1H), 7.55–7.65 (m, 2H), 6.90–6.95 (m, 1H), 6.75–6.85 (m, 2H), 6.55–6.60 (m, 1H), 6.30–6.35 (br s, 3H), 6.25–6.35 (m, 1H), 4.45–4.65 (m, 1H), 3.90–4.20 (m, 4H), 2.10 (s, 3H). MS: *m/z* 419 (M+1). Anal. Calcd for $C_{19}H_{19}FN_4O_4S$: C, 54.54; H, 4.58; N, 13.39. Found: C, 54.91; H, 4.84; N, 13.70. **14b**: ^{1}H NMR: δ 10.00 (br s, 1H), 7.85–7.95 (m, 2H), 7.15–7.25 (m, 1H), 7.00–7.10 (m, 2H), 6.75–6.70 (m, 1H), 6.45–6.40 (m, 1H), 6.25–6.35 (br s, 3H), 4.55–4.65 (m, 1H), 3.90–4.25 (m, 4H), 2.15 (s, 3H). MS: *m/z* 435 (M+1). Anal. Calcd for $C_{19}H_{19}FN_4O_3S_2$: C, 52.52; H, 4.41; N, 12.89. Found: C, 52.76; H, 4.63; N, 13.08. **15a**: ^{1}H NMR: δ 9.95 (br s, 1H), 7.70–7.75 (br s, 1H), 7.55–7.65 (m, 2H), 6.95–7.00 (m, 1H), 6.80–6.85 (m, 2H), 6.30–6.60 (m, 2H), 4.40–4.50 (m, 1H), 3.90–4.25 (m, 4H), 3.85 (s, 3H), 2.05 (s, 3H). MS: *m/z* 434 (M+1). Anal. Calcd for $C_{20}H_{20}FN_3O_5S$: C, 55.42; H, 4.65; N, 9.69. Found: C, 55.87; H, 4.89; N, 9.77. **15b**: ^{1}H NMR: δ 10.05 (br s, 1H), 7.85–7.90 (m, 2H), 7.70–7.80 (br s, 1H), 7.15–7.25 (m, 1H), 7.00–7.10 (m, 2H), 6.40–6.75 (m, 2H), 4.35–4.50 (m, 1H), 3.85–4.25 (m, 4H), 3.80 (s, 3H), 2.10 (s, 3H). MS: *m/z* 450 (M+1). Anal. Calcd for $C_{20}H_{20}FN_3O_4S_2$: C, 53.44; H, 4.48; N, 9.35. Found: C, 53.23; H, 4.39; N, 9.04. **16a**: ^{1}H NMR: δ 10.00 (br s, 1H), 7.55–7.65 (m, 2H), 6.75–7.00 (m, 4H), 6.30–6.60 (m, 2H), 4.30–4.45 (m, 1H), 3.85–4.25 (m, 4H), 3.25 (s, 6H), 2.10 (s, 3H). MS: *m/z* 447 (M+1). Anal. Calcd for $C_{21}H_{23}FN_4O_4S$: C, 56.49; H, 5.19; N, 12.55. Found: C, 56.31; H, 4.96; N, 12.29. **16b**: ^{1}H NMR: δ 9.95 (br s, 1H), 7.80–7.90 (m, 2H), 7.05–7.25 (m, 3H), 6.75–6.80 (br s, 1H), 6.45–6.75 (m, 2H), 4.30–4.45 (m, 1H), 3.80–4.30 (m, 4H), 3.30 (s, 6H), 2.15 (s, 3H). MS: *m/z* 463 (M+1). Anal. Calcd for $C_{21}H_{23}FN_4O_3S_2$: C, 54.53; H, 5.01; N, 12.11. Found: C, 54.78; H, 5.27; N, 12.44. **17a**: ^{1}H NMR: δ 10.10 (br s, 1H), 7.55–7.65 (m, 2H), 6.95–7.00 (m, 1H), 6.80–6.85 (m, 2H), 6.30–6.60 (m, 2H), 5.55–5.65 (br s, 4H), 4.55–4.65 (m, 1H), 3.90–4.30 (m, 4H), 2.15 (s, 3H). MS: *m/z* 434 (M+1). Anal. Calcd for $C_{19}H_{20}FN_5O_4S$: C, 52.65; H, 4.65; N, 16.16. Found: C, 52.96; H, 4.87; N, 16.22. **17b**: ^{1}H NMR: δ 10.05 (br s, 1H), 7.85–7.95 (m, 2H), 7.10–7.25 (m, 3H), 6.40–6.75 (m, 2H), 6.60–6.65 (br s, 4H), 4.55–4.65 (m, 1H), 3.90–4.35 (m, 4H), 2.10 (s, 3H). MS: *m/z* 450 (M+1). Anal. Calcd for $C_{19}H_{20}FN_5O_3S_2$: C, 50.77; H, 4.48; N, 15.58. Found: C, 50.45; H, 4.29; N, 15.37. **18a**: ^{1}H NMR: δ 9.95 (br s, 1H), 7.60–7.70 (m, 2H), 6.80–7.00 (m, 5H), 6.25–6.60 (m, 2H), 4.40–4.50 (m, 1H), 3.85–4.25 (m, 4H), 2.10 (s, 3H), 1.70–1.75 (m, 1H), 1.35–1.55 (m, 4H). MS: *m/z* 459 (M+1). Anal. Calcd for $C_{22}H_{23}FN_4O_4S$: C, 57.63; H, 5.06; N, 12.22. Found: C, 57.47; H, 4.85; N, 12.01. **18b**: ^{1}H NMR: δ 9.90 (br s, 1H), 7.85–7.95 (m, 2H), 7.10–7.25 (m, 3H), 6.90–6.95 (br s, 2H), 6.45–6.80 (m, 2H), 4.40–4.50 (m, 1H), 3.85–4.30 (m, 4H), 2.05 (s, 3H), 1.40–1.75 (m, 5H). MS: *m/z* 475 (M+1). Anal. Calcd for $C_{22}H_{23}FN_4O_3S_2$: C, 55.68; H, 4.88; N, 11.81. Found: C, 55.96; H, 5.04; N, 11.95.

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