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Synthesis and antibacterial activity of new chiral *N*-sulfamoyloxazolidin-2-ones

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Abstract. A new series of *N*, *N*′-bis-oxazolidinones-sulfone and 5-chloromethylsulfamoyl-oxazolidin-2-ones have been synthesized in three steps (carbamoylation, sulfamoylation and cyclization) starting from 1,3-dichloroporopan-2-ol, chlorosulfonyl isocyanate and primary or secondary amines. Synthesis has been carried out following simple methodology in excellent isolated yields. The structure and purity of the original compounds were confirmed by IR, NMR, and MS. The compounds were evaluated for their *in vitro* antibacterial activity against some Gram-positive bacteria; *Staphylococcus aureus* and Gram-negative bacteria; *Escherichia Coli, Klebsiella pneumonieae, Acinetobacter, Pseudomonas aeruginosa, Enterococcus, Salmonella sp.* The compounds showed moderate to good antibacterial activity.

Keywords. Oxazolidinone; chlorosulfonyl isocyanate; sulfonamide; antibacterial activity.

1. Introduction

Infections caused by bacteria pose a serious challenge to the medical community and highlight the importance and urgent need for new potent antimicrobial agents. The oxazolidinones are an important class of antibiotic that has been discovered and successfully implemented in the clinic over the past 40 years.[1] Linezolid derivatives emerged in 1996 as a result of intensive investigations at pharmacy[2] and it was approved by FDA in 2000. It has been used to treat a number of resistant strains of bacteria (e.g., methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*).[3] However, the emergence of linezolid's resistance has been reported, initially in *Enterococcus* species.[4] More recently, resistant strains of MRSA,[5] *E. coli*[6] and other bacteria[7] have also been identified.

On the other hand, the sulfonamide moiety is present in a number of compounds which show diverse biological activities. Some of these activities include antibacterial, hypoglycemic, diuretic, anti-hypertensive, carbonic anhydrase inhibitors and antiviral drugs are among several examples.[8–18] They inhibit the activity of the enzyme dihydropteroate synthase (DHPS),[19] preventing the synthesis of folic acid (Vitamin B9), an intermediate necessary for life of certain bacteria.

In the literature novel oxazolidinones containing sulfonamide moiety have been described which have interesting biological properties. Sulfonamide-oxazolidinones were first described for their utility for treating plant diseases such as Sulfoxide 1. Antibacterial properties were discovered six years later, specifically, sulfonamide 2 exhibited modest efficacy against several strains of bacteria (figure 1).[20]

In this work, we describe the synthesis and antibacterial activity of oxazolidinones having sulfonamide moiety (scheme 1). We report the synthesis of novel *N*-sulfamoyl-oxazolidinones (**5a-f**) starting from chlorosulfonyl isocyanate by three steps: carbamoylation, sulfamoylation and cyclization. We have investigated the antibacterial activity of *N*-sulfamoyloxazolidinones (**5a, c-e**) against representatives strains of gram-positive *Staphylococcus aureus* ATCC 25923 (Sa), *Staphylococcus aureus (clinical isolate) and* gram-negative, *Escherichia coli* ATCC 25922 (E.coli), *Escherichia coli* (clinical isolate), *Klebsiella pneumonieae* (clinical isolate) (Kp), *Acinetobacter sp* (clinical isolate) (Ac), *Pseudomonas aeruginosa* (clinical isolate) (Pa), *Enterococcus sp* (clinical isolate) (Entero), *Salmonella sp* (clinical

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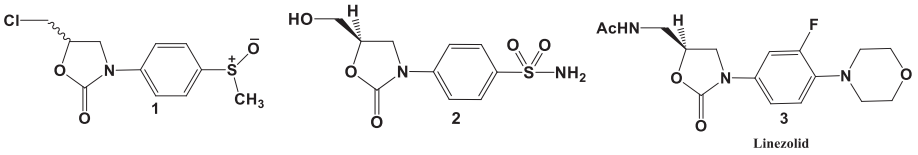
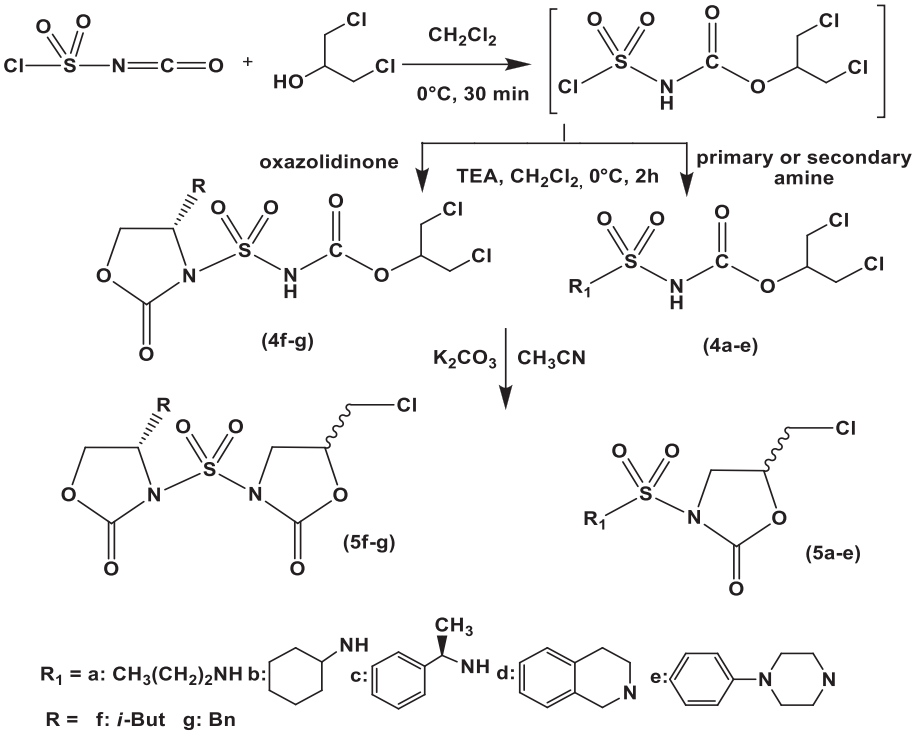


Figure 1. Oxazolidinone with sulfonamide group.



Scheme 1. Preparation of *N*-sulfamoyl oxazolidinones.

isolate) (Salmo), ATCC 27853 and *Pseudomonas aeruginosa* (Salmo) by disc diffusion methods.

2. Experimental

2.1 *Materials and Methods*

Melting points were determined in open capillary tubes on an Electro thermal apparatus and uncorrected. IR spectra were recorded on a Perkin Elmer FT-600 spectrometer. ^{1}H NMR spectra were recorded with a 360 WB or AC 250-MHz Bruker spectrometer using DMSO-d6 or $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts are reported in δ units (ppm). All coupling constants J are reported in hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and combination of these signals. Electron ionization mass spectra (30 eV) were recorded in positive or negative mode on Water Micro Mass ZQ. HRMS were recorded on a JEOL JMSDX-300 using NBA as matrix in FAB^+ ionization mode. All reactions were monitored by TLC on silica Merck h60 F (Art. 5554) precoated aluminium plates and were developed by spraying with ninhydrin solution. The visualization was made with ultraviolet light. Chromatography column was performed on Merck silica gel 60H (Art. 9385).

Clinical isolates from parietal distal takings of patients. *Staphylococcus aureus*, *Escerichia coli*, *Acinetobacter sp*, *Pseudomonas aeruginosa, Enterococcus sp, Salmonella sp* and *Klebseilla pneumoniae* cultures were obtained from the laboratory of virology-bacteriology of Hospitalo-Universities Center Benflis Touhami Batna. We used, as control, three referenced strains: *Staphylococcus aureus* ATCC 259**23**, *Escerichia coli* ATCC 259**22** and *Pseudomonas aeruginosa* ATCC 278**53**.

Minimal inhibitory concentrations (MIC) were determined by the micro dilution broth method following the procedures of National Committee for Clinical Laboratory Standard.[21] MIC is defined as the lowest concentration of the antimicrobial agents that inhibited visible growth of the micro-organism. All tests were performed in Mueller Hinton Broth (MHB). The compounds under the test were dissolved in analytically

pure dimethylsulfoxide (DMSO) and geometric dilutions ranging from 0.97 to 500 lg/mL of the compounds.

Inhibition zones of (**5a, c-e**) were determined by the disk diffusion method.[8] The culture suspensions were prepared and adjusted by comparing against 0.3 McFarland turbidity tubes. Mueller–Hinton Agar (20 mL) was poured into each sterile Petri dish after injecting cultures (100 μL) of microorganisms and distributing medium in Petri dish homogeneously. The compounds were dissolved in DMSO of 10 mg/mL to prepare stock solution. Empty sterilized disks of 6 mm were impregnated with 50 μL of compounds at the required concentrations of 0.97–500 μg/mL.[22,23] Disks were placed on agar plates and the cultures were incubated at 37°C for 24 h. The evaluation of the inhibition zones formed on the medium was in mm. The reference disks used for control are ciprofloxacin, Ac nalidixique and Ofloxacine.

To ensure that the solvent had no effect on the bacterial growth, a control was performed at the test medium supplemented with DMSO at the same dilutions as used in the experiments.

2.2 *General procedure for the synthesis of carboxylsulfamides*

To a stirred solution of chlorosulfonyl isocyanate (CSI) (1.62 g, 11.44 mmol) in 10 mL of anhydrous dichloromethane at 0°C added (1.47 g, 11.39 mmol) of 1,3-dichloropropanol-2 in the same solvent. After 30 min, the resulting solution and (1.75 mL, 1.1 equiv) of triethylamine was slowly added into the solution containing 1 equiv of primary or secondary amine or oxazolidinone in (10 mL) of dichloromethane. The reaction did not rise above 5°C. The resulting reaction solution was allowed to warm up to room temperature for over 2 h. The reaction mixture was diluted with 30 mL of dichloromethane, washed with 0.1 N HCl and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to give the crude product. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 9.9/0.1) to give a carboxylsulfamides in good yields.

2.2a *N-propyl 1, 3-dichloropropan-2-yl sulfonamide carbamate **4a***: Yield: 95%; M.p. = 114-116°C; R_f = 0.69 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 7.67 (s, 1H, NH=CO); 5.15 (m, 1H, CH-CH_2-Cl); 5.01 (t, J = 6.0 Hz, 1H, NH); 3.71 (d, J = 6.0 Hz, 4H, 2CH_2-Cl); 3.01 (q, J = 9.0, Hz, 2H, CH_2-NH); 1.55 (m, 2H, CH_2-CH_3); 0.90 (t, J = 9.0 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ ppm): 149.1; 73.1; 44.6; 41.5; 41.1; 21.3; 10.0. IR (KBr, ν/cm^{-1}): 3261 and 3155 (2NH); 1750 (C=O); 1375 and 1157 (SO_2). SM ESI$^+$: 294 [M+H] $^+$ calcd. for M = 293 [$C_7H_{14}Cl_2N_2O_4S$].

2.2b *N-cyclohexyl, 1, 3-dichloropropan-2-yl sulfonamide carbamate **4b***: Yield: 94%; M.p. = 119-121°C; R_f = 0.71 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 7.65 (s, 1H, NH-*C* = *O*); 5.15 (m, 1H, CH-CH_2-Cl); 3.78 (d, J = 6.0 Hz, 4H, 2CH_2-Cl); 3.30 (m, 1H, CH-NH); 1.95 (m, 2H, CH_2cyc); 1.73 (m ,2H, CH_2-cyc); 1.33 (m, 6H, 3CH_2-cyc). ^{13}C NMR ($CDCl_3$, δ ppm): 150.2; 76.5; 42.2; 42.1; 33.2; 24.6; 24.5. IR (KBr, ν/cm^{-1}): 3265 and 3169 (2NH); 1755 (C=O); 1374 and 1156 (SO_2). SM ESI$^+$: 334 [M+H] $^+$100 % calcd. for M = 333 [$C_{10}H_{18}Cl_2N_2O_4S$].

2.2c *N-(R)1-methylbenzyl,1,3-dichloropropan-2-ylsulfonamide carbamate **4c***: Yield: 90%; M.p. = 124-126°C; R_f = 0.70 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 7.95 (s, 1H, NH-*C* = *O*); 7.50-7.25 (m, 5H, H-Ar); 5.95 (d, J = 7.8 Hz, 1H, NH); 4.95 (m, 1H, CH-CH_2_Cl); 4.65 (m, 1H, CH*); 3.70 (d, J = 7.0 Hz, 2H, CH_2-Cl); 3.60 (d, J = 6.7 Hz, 2H, CH_2-Cl); 1.55 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ ppm): 143.4; 134.8; 122.6; 122.3; 119.7; 67.2; 48.1; 39.4; 16.5. IR (KBr, ν/cm^{-1}): 3256 and 3140 (2NH); 1753 (C=O); 1657 (C=C); 1370 and 1158 (SO_2).SM ESI$^+$: 356 [M+H] $^+$100 % calcd. for M = 355 [$C_{12}H_{16}Cl_2N_2O_4S$].

2.2d *3,4-dihydroisoquinolin-2(1H)-yl,1,3-dichloropropan-2-yl sulfonyl carbamate **4d***: Yield: 82%; oil; R_f = 0.63 (CH_2Cl_2 /MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 7.80 (s, 1H, NH-*C* = *O*); 7.20-7.00 (m, 4H, H-Ar); 5.10 (m, 1H, CH-CH_2-Cl); 4.60 (s, 2H, Ph-CH_2-N); 3.80-3.60 (m, 6H, CH_2-CH_2-N-cyc + 2CH_2-Cl_2); 2.90 (t, J = 5.8 Hz, 2H, Ph-CH_2-CH_2). ^{13}C NMR ($CDCl_3$, δ ppm): 159.0; 136.1; 134.1; 127.5; 126.9; 126.3; 125.7; 78.8; 47.4; 45.0; 44.3; 28.1. IR (CCl_4, ν/cm^{-1}): 3262 (NH); 1751 (C=O); 1374 and 1159 (SO_2). SM ESI$^+$: 367.1 [M+H] $^+$, 390.1 [M+Na] $^+$ calcd. for M = 367 [$C_{13}H_{16}Cl_2N_2O_4S$].

2.2e *Phenylpeperazinyl, 1,3-dichloropropan -2-yl sulfonamide carbamate **4e***: Yield: 85%; M.p. = 136-138°C; R_f = 0.68 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 7.60 (s, 1H, NH-*C* = *O*); 7.35-6.90 (m, 5H, H-Ar); 5.20 (m, 1H, CH-CH_2-Cl); 3.90 (d, J = 5.2 Hz, 4H, 2CH_2-Cl_2); 3.65 (t, J = 5.2 Hz, 4H, 2Ph-N-CH_2); 3.30 (t, J = 5.4 Hz, 4H, 2CH_2-N). ^{13}C NMR ($CDCl_3$, δ ppm): 159.0; 149.6; 129.6; 121.9, 114.3; 78.8; 51.5; 45.8; 45.0. IR (KBr, ν/cm^{-1}): 3260 (NH); 1739 (C=O); 1372 and 1167 (SO_2). SM ESI$^+$: 397 [M+H] $^+$100% calcd. for M = 396 [$C_{14}H_{19}Cl_2N_3O_4S$].

2.2f *(S)4-isobutyl-2-oxooxazolidin-3-yl, 1,3-dichloropropan-2-yl sulfonylcarbamate* ***4f***: Yield: 91 %; M.p. = 132-134°C; R_f = 0.67 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 8.00 (s, 1H, NH-*C* = *O*); 4.90 (m, 1H, CH-CH_2–Cl); 4.60 (m, 1H, *CH); 4.50 (dd, J = 5.9, J = 7.8 Hz, 1H, HCHO); 4.15 (dd, J = 5.2, J = 7.3 Hz, 1H, HCHO); 3.75 (d, J = 5.2 Hz, 4H, 2CH_2-Cl); 1.95 (m, 1H, CH*i-But*); 1.68 (m, 2H, CH_2*i-But*); 0.98 (2d, J = 8.0 Hz, 6H, 2CH_3*i-But*). ^{13}C NMR ($CDCl_3$, δ ppm): 152.5; 150.5; 76.9; 65.0; 44.9; 43.2; 42.0; 24.7; 23.0. IR (KBr, ν/cm^{-1}): 3266 (NH); 1756 (C=O); 1375 and 1156 (SO_2). SM ESI$^+$: 378 [M+H]$^+$ calcd. for M = 377 [$C_{11}H_{18}Cl_2N_2O_6S$].

2.2g *(S)4-benzyl-2-oxooxazolidin-3-yl, 1,3-dichloropropan-2-yl sulfonylcarbamate* ***4g***: Yield: 88%; M.p. = 128-130°C; R_f = 0.65 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 8.10 (s, 1H, NH-*C* = *O*); 7.45-7.30 (m, 5H, H-Ar); 5.00 (m, 1H, CH-CH_2-Cl); 4.57 (m, 1H, *CH); 4.40 (dd, J = 13.0 Hz, J = 12.0 Hz, 1H, HCHO); 4.15 (dd, J = 13.1 Hz, J = 12.3 Hz, 1H, HCHO); 3.70 (d, J = 6.0 Hz, 4H, 2CH_2-Cl); 3.20 (dd, J = 10.3 Hz, J = 13.0 Hz, 1H, HCH-Ph); 3.00 (dd, J = 13.6 Hz, J = 10.0 Hz, 1H, HCH-Ph). ^{13}C NMR ($CDCl_3$, δ ppm): 159.0; 152.1; 138.4; 128.4; 128.0; 126.3; 78.0; 65.0; 47.8; 44.8; 40.0. IR (KBr, ν en cm^{-1}): 3269 (NH); 1754 (C=O); 1457(C=C); 1370 and 1160 (SO_2). SM ESI$^+$: 412 [M+H] $^+$ calcd. for M = 411 [$C_{14}H_{16}Cl_2N_2O_6S$].

2.3 *General procedure for the synthesis of sulfamoyloxazolidinones*

A solution of carboxylsulfamides (0.47 g, 1.28 mmol) in dry CH_3CN (20 mL) or acetone was added to K_2CO_3 (0.17 g, 1.23 mmol). The reaction mixture was stirred at room temperature under inert atmosphere. Progress of the reaction is monitored by TLC, which indicates complete disappearance of carboxylsulfamide within 1.5 h. Then the reaction mixture was filtered and concentrated under vacuum to give the crude product.

2.3a *5-(chloromethyl) N-propyl-oxazolidin-2-one-3-sulfonamide* ***5a***: Yield: 98%; M.p. = 139-141°C; R_f = 0.73 (CH_2Cl_2/Me OH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 5.36 (t, J = 8.0 Hz, 1H, NH); 4.90 (m, 1H, *CH-CH_2-Cl); 4.18 (t, J = 9.0 Hz, 1H, HCH-Cl); 3.95 (dd, J = 6.0 Hz, 1H, HCH-Cl); 3.80-3.65 (2dd (ABX system), J = 6.0, J = 5.2, J = 3.0 Hz, 2H, CH_2ox); 3.10 (q, J = 9.0 Hz, 2H, CH_2-NH); 1.64 (m, 2H, CH_2-CH_3); 0.97 (t, J = 9.0 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, δ ppm): 150.2; 71.3; 46.9; 45.0; 43.5; 21.7; 10.2. IR (KBr, ν /cm^{-1}): 3250 (NH); 1755 (C=O); 1350 and 1144 (SO_2). SM ESI$^+$ 30 eV m /z: 257.4 [M+H] $^+$100%, 259.4 [M+3]$^+$ calcd. for M = 256.5 [$C_7H_{13}ClN_2O_4S$].

2.3b *5-(chloromethyl)-N-cyclohexyl-oxazolidin-2one-3-sulfonamide* ***5b***: Yield: 96%; M.p. = 143-145°C; R_f = 0.75 (CH_2Cl_2/Me OH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 5.25 (d, J = 6.0 Hz, 1H, NH); 4.80 (m, 1H, *CH-CH_2-Cl); 4.11 (t, J = 6.0 Hz, 1H, HCH-Cl); 3.91 (dd, J = 6.0 Hz, 1H, HCH-Cl); 3.80-3.60 (2dd (ABX system), J = 6.0, J = 5.2, J = 3.0 Hz, 2H, CH_2ox); 3.23 (m, 1H, CH-NH); 1.90 (m, 2H, CH_2-cyc); 1.68 (m, 2H, CH_2-cyc); 1.25 (m, 6H, 3CH_2-cyc). ^{13}C NMR ($CDCl_3$, δ ppm): 149.8; 69.4; 51.7; 45.2; 41.9; 30.9; 30.7; 22.5; 22.1; 22.0. IR (KBr, ν /cm^{-1}): 3245 (NH); 1730 (C=O); 1319 and 1184 (SO_2). SM ESI$^+$ 30 eV m /z: 297.5 [M+H] $^+$100%, 299.5 [M+3]$^+$ calcd. for M = 296.5 [$C_{10}H_{17}ClN_2O_4S$].

2.3c *5-(chloromethyl), N-((R)-1-methyl benzyl)oxazolidin-2one-3-sulfonamide* ***5c***: Yield: 97%; M.p. = 149-151°C. R_f = 0.74 (CH_2Cl_2/Me OH: 9/1). ^{1}H NMR (DMSO-d_6, δ ppm): 9.30 (s, 1H, NH); 7.50-7.20 (m, 5H, H-Ar); 4.70 (m, 1H, *CH-CH_2-Cl); 4.50 (q, J = 6.8 Hz 1H, CH*); 3.95 (t, J = 9.0 Hz, 1H, HCH-Cl); 3.80 (dd, J = 3.1, J = 4.2 Hz, 1H, HCH-Cl); 3.75-3.55 (2dd (ABX system), J = 4.3, J = 3.6, J = 5.9 Hz, 2H, CH_2ox); 1.40 (d, J = 5.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6, δ ppm): 151.0; 144.9; 129.6; 127.8; 127.0; 82.3; 50.3; 43.7; 35.9; 21.8 IR (KBr, ν /cm^{-1}): 3253 (NH); 1729 (C=O); 1320 and 1178 (SO_2). SM ESI$^+$ 30 eV m /z: 319.4 [M+H] $^+$, 321.3 [M+3]$^+$ calcd. for M = 318.5 [$C_{12}H_{15}ClN_2O_4S$].

2.3d *5-(chloromethyl)-3-((3,4-dihydroisoqui-nolin-2(1H)-yl) sulfonyl)-1,3-oxazolidin-2-one* ***5d***: Yield: 95%; M.p. = 92–94°C; R_f = 0.67 (CH_2Cl_2 /MeOH: 9/1). ^{1}H NMR (DMSO-d_6, δ ppm): 7.20-7.00 (m, 4H, H-Ar); 4.90 (m, 1H, *CH-CH_2-Cl); 4.60 (s, 2H, Ph-CH_2-N-cyc); 4.20 (t, J = 9.4 Hz, 1H, HCHCl); 3.95 (dd, J = 5.8 Hz, 6.0 Hz, HCHCl); 3.70 (m, 4H, CH_2O + CH_2-CH_2-N-cyc); 3.0 (t, J = 5.9 Hz, 2H, Ph-CH_2-CH_2). ^{13}C NMR (DMSO-d_6, δ ppm):152.1; 134.9; 127.3; 126.8; 126.5;125.5; 80.3; 51.0; 50.0; 44.3; 34.4; 26.0. IR (KBr, ν /cm^{-1}): 1750 (C=O); 1360 and 1150 (SO_2). SM ESI$^+$ 30 eV m /z: 331.2 [M+H]$^+$100%, 333.2 [M+3]$^+$, 353.1 [M+Na]$^+$35% calcd. for M = 330.5 [$C_{13}H_{15}ClN_2O_4S$].

2.3e *5-(chloromethyl)-3-((4-phenylpiperazin -1-yl)sulfonyl)-1, 3-oxazolidin-2-one* ***5e***: Yield: 91%; M.p. = 126-128°C; R_f = 0.72 (CH_2Cl_2/Me OH: 9/1). ^{1}H NMR (DMSO-d_6, δ ppm): 7.40-6.90 (m, 5H, H-Ar); 4.95 (m, 1H, *CH-CH_2-Cl); 4.25 (t, J = 9.4 Hz, 1H, HCHCl); 4.02 (dd, J = 5.5 Hz, 1H, HCHCl); 3.80-3.65 (2dd, (ABX system), J = 5.0, J = 3.3, J = 3.4 Hz, 2H,

CH_2O); 3.62 (t, $J = 5.2$, $J = 4.8$ Hz, 4H, 2 Ph-CH_2-N); 3.25 (t, $J = 4.8$, 5.2 Hz, 4H, 2 CH_2-CH_2-N). ^{13}C NMR (DMSO-d_6, δ ppm): 151.9; 149.9; 129.6; 121.9; 114.3; 81.4; 50.3; 43.7; 43.3; 32.9. IR (KBr, ν /cm^{-1}): 1739 (C=O); 1310 and 1143 (SO_2). SM ESI$^+$ 30 eV m /z: 360.1 [M+H] $^+$100%, 362.0 [M+3]$^+$, calcd. for M = 359.5 [$C_{14}H_{18}ClN_3O_4S$].

2.3f *5-(chloromethyl)-3-(((S)4-isobutyl-2-oxooxazolidin-3-yl)sulfonyl)oxazolidin-2-one* ***5f***: Yield: 90%; M.p. = 141-143°C; R_f = 0.72 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 4.91 (m, 1H, *CH-CH_2-Cl); 4.55-4.10 (m, 3H, *CH+CH_2O); 4.05 (t, $J = 5.2$, $J =$ 6.5 Hz, 1H, HCH-Cl); 3.84 (dd, $J = 5.1$, $J = 6.0$ Hz, 1H, HCH-Cl); 3.80-3.50 (2dd (ABX system), $J = 9.5$, $J = 8.0$, $J = 5.8$ Hz, 2H, CH_2-Nox), 1.93 (m, 1H, CH-*iBut*); 1.65 (m, 2H, CH_2-*iBut*); 0.98 (2d, $J = 9.8$ Hz, 6H, 2CH_3-*iBut*). ^{13}C NMR ($CDCl_3$, δ ppm): 152.9; 151.0; 81.9; 65.6; 43.9; 43.2; 42.7; 35.9; 24.7; 23.0. IR (KBr, ν /cm^{-1}): 1735 (C=O); 1315 and 1177 (SO_2). SM ESI$^+$: 363.0 [M+Na]$^+$, 341.1 [M+H]$^+$100 %, 343.0 [M+3]$^+$, calcd. for M = 340.5 [$C_{11}H_{17}ClN_2O_6S$].

2.3g *5-(chloromethyl)-3-(((S)4-benzyl-2-oxooxazolidin-3-yl)sulfonyl)oxazolidin-2-one* ***5g***: Yield: 9%; M.p. = 146-148°C. R_f = 0.69 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR ($CDCl_3$, δ ppm): 7.45-7.30 (m, 5H, H-Ar); 4.90 (m, 1H, *CH-CH_2-Cl); 4.60 (m, 1H, *CH); 4.45 (dd, $J = 13.4$ $J = 10.5$ Hz, 1H, HCHO); 4.20 (dd, $J =$ 13.4 Hz, $J = 10.0$ Hz, 1H, HCHO); 4.10 (t, $J = 6.5$ Hz, 1H, HCH-Cl); 3.85 (dd, $J = 6.5$ Hz, 1H, HCH-Cl); 3.80-3.55 (2dd (ABX system), $J = 4.85$, $J = 5.8$, $J =$ 5.1, 2H, CH_2-N); 3.17 (dd, $J = 10.3$ Hz, $J = 13.6$ Hz, 1H, HCH-Ph); 3.01 (dd, $J = 13.6$ Hz, $J = 10.0$ Hz, 1H, HCH-Ph). ^{13}C NMR ($CDCl_3$, δ ppm): 152.0; 151.1; 138.0; 128.7; 128.0; 126.3; 81.0; 65.0; 47.0; 43.8; 40.4; 35.8. IR (KBr, ν /cm^{-1}): 1739 (C=O); 1447(C=C); 1323 and 1175 (SO_2). SM ESI$^+$: 375.4 [M+H]$^+$, 377.4 [M+3]$^+$calcd. for M = 374.5 [$C_{14}H_{15}ClN_2O_6S$].

3. Results and Discussion

3.1 *Synthesis of N-sulfamoyloxazolidinones*

The starting compounds **5a–c** were easily prepared in excellent yield (90–97%), using chlorosulfonyl isocyanate CSI, that is the suitable available reagent allowing the introduction of a sulfonamide moiety.[24–30] The synthesis passed through three steps (carbamoylation, sulfamoylation and cyclization) starting from a prochiral alcohol. Carbamoylation: The prochiral alcohol, 1,3-dichloro-2-propanol reacted smoothly with chlorosulfonyl isocyanate in the presence of dichlo romethane to easily give carbamate. Sulfamoylation: The condensations of the carbamate with oxazolidinones or commercially available corresponding amines in the presence of triethylamine at 0°C afforded substituted sulfamides (**1a-g**) in good yields. Cyclization: The cyclization of compounds (**1a-fg**) with potassium carbonate in acetonitrile at room temperature yielded *N*, *N′*-bis-oxazolidinones-sulfone and 5-chloromethyl-2-oxazolidinone derivatives amines with a chiral center at the 5-position. The structures of all synthesized compounds were unambiguously confirmed by usual spectroscopic methods ^{1}H NMR, ^{13}C NMR, mass spectrometry and IR.

3.2 *In vitro antibacterial activity*

During our study, the antibacterial activity of compounds was screened *in vitro* against various pathogens by using disk diffusion and micro dilution methods. Ciprofloxacin, Ac nalidixique and Ofloxacine were used as positives controls. The solvent control (DMSO) did not show any antimicrobial activity (negative control). The results for the synthesized compounds are shown in figure 2. As seen in figure 2, a good activity was obtained with **5a**, **5c** and **5d**, no activity was obtained with **5e**. For the first three molecules, no

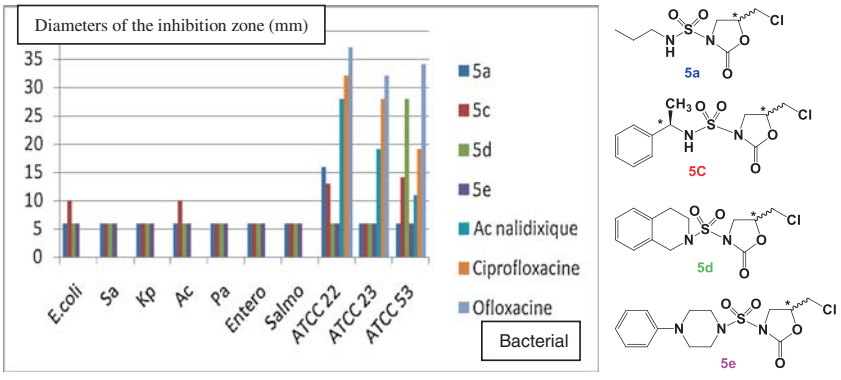


Figure 2. Diameters of zone inhibition of the bacterial strains obtained with *N*-sulfamoyl oxazolidinones 5c, 5a, 5d and 5e at 500μg/mL.

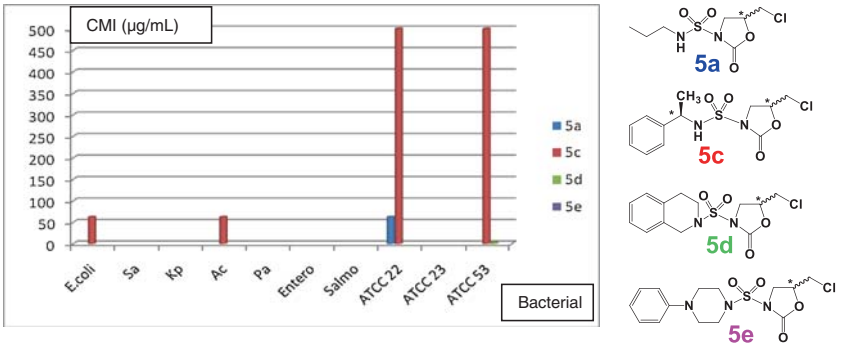


Figure 3. Results of the MIC of the various bacterial strains for the *N*-sulfamoyl oxazolidinones **5a, 5c, 5d** and **5e**.

activity was observed on the gram positive bacteria (Kp, pa, entero, salmo, *Staphylococcus aureus clinical isolated* and ATCC 259**23**).

5a showed an antibacterial activity against gram negative referenced bacteria *E. coli* ATCC 259**22**. The inhibitory diameters varied between 8 and 16 mm for concentrations from 62.5 to 500gμg/mL. The inhibitory diameters of **5c** varied between 10 and 14 mm with concentrations from 62.5 to 500 μg/mL for clinical isolated *Escerichia coli* and *E.coli* ATCC 259**22**, *Acinetobacter* and *Pseudomonas aeruginosa* ATCC53. The clinical isolated *Acinetobacter* was multi-resistant notably for imipeneme. **5d** has higher diameters going upto 28 mm for *Pseudomonas aeruginosa* ATTC53 with concentration between 3.9 and 500 μg/mL (figure 3).

4. Conclusions

In summary, a new series of *N*, *N*′-bis-oxazolidinones-sulfone and 5-chloromethylsulfamoyl-oxazolidinone derived from amines were synthesized in good yield starting from prochiral 1,3-dichloro-2-propanol and chlorosulfonyl isocyanate. This strategy involves the formation of carboxylsulfamide by carbamoylation-sulfamoylation reaction followed by intermolecular cyclization. The structures of all the synthesized compounds were unambiguously confirmed by ^{1}H NMR, ^{13}C NMR, mass spectrometry and IR. All compounds except **5e** demonstrated an activity on clinical isolate and referenced gram negative bacteria. Consequently, these synthesized compounds may be suggested for industrial applications.

Supplementary Information

All additional information pertaining to characterization of the *N*-sulfamoyloxazolidin-2-ones using ESI-MS technique (figures S14, S15), ^{1}H NMR spectrum (figures S8, S10, S12, S13), ^{13}C NMR spectrum (figures S9, S11), are given in the supporting information which available at www.ias.ac.in/chemsci.

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