Synthesis and Biological Activity of New Chiral N-Acylsulfonamide Bis-oxazolidin-2-ones

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[a]Laboratoire de Chimie Organique Appliquée, Groupe de Chimie Bioorganique, Université Badji Mokhtar, Annaba, BP 12, Algeria
[b]Laboratoire de Toxicologie Cellulaire, Universite Badji Mokhtar, Annaba, BP 12, Algeria
[c]Laboratoire de Chimie Bioorganique et Bionanomatériaux, CSPBAT, FRE 3043 CNRS, Université Paris 13, Bobigny Cedex, France
[d]Institut des Sciences Moléculaires de Marseille, UMR 7313 CNRS and Université d'Aix Marseille, Faculté des Sciences et Techniques de Saint Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France
*E-mail: noureddineaouf@yahoo.fr

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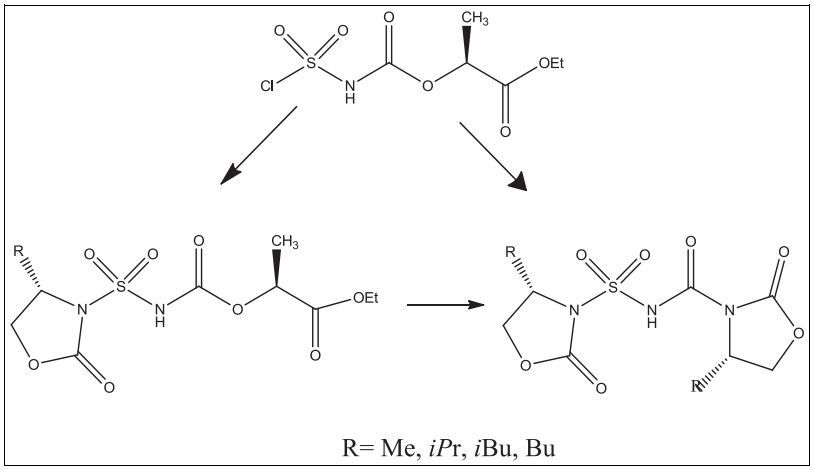

A new series of chiral 5-substituted bis-oxazolidinones containing an acylsulfonamide moiety has been synthesized starting from chlorosulfonyl isocyanate, (L)-ethyl lactate, and oxazolidin-2-ones. All the reactions were conducted at ambient temperature, and the *N*-acylsulfonamide bis-oxazolidin-2-ones were obtained with high yields within 2 h. Some of the newly synthesized compounds were evaluated *in vitro* against the virulent strain RH of *Toxoplasma gondii* and the human lymphocytes, and showed promising results.

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INTRODUCTION

Substituted acylsulfonamides have been widely used as carboxylic acid bioisosteres in medicinal chemistry because of their comparable acidity [1].

They have received considerable attention because of their diverse biological activities as precursors of therapeutic agents for Alzheimer's disease [2], as antibacterial inhibitors of tRNA synthetases [3], as antagonists for angiotensin II [4], as leukotriene D_4-receptors [5], and as protease inhibitors [6]. Some of these compounds were employed for designing many types of therapeutic agents. Some clinically used HIV protease inhibitors possess sulfonamide moieties in their structure. In addition, several *N*-acyl-*N*-(2,3,4,5,6-pentafluorophenyl) methane sulfonamide have been used as chemoselective N-acylating reagents [7]. Katritzky et *al.* [8] reported N-acylation of sulfonamides using *N*-acyl benzotriazole as an acylating agent. A very large number of other derivatives are constantly being synthesized and evaluated to obtain compounds with lower toxicity or increased activity against viruses resistant to such first-generation drugs. The synthesis of *N*-acylsulfonamide **1**, which is an analogue of β-aspartyl-AMP, is described [9]. This compound appears to be the first potent inhibitor of human asparagine synthetase.

Also, the synthesis of acylsulfonamides using a convenient method with polymer-supported reagents has been described [10]. The preparation of *N*-acylsulfonamides is described [11] using silica sulfuric acid as an efficient catalyst under both solvent-free and heterogeneous conditions. However, some of the aforementioned methods suffer from one or more of the following disadvantages: long reaction time, low product yield, or no stereoselectivity.

In our previous work, we have reported the synthesis of chiral *N*,*N*′-sulfonyl bis-oxazolidin-2-ones **2** [12]. Pursuing our interest in modified bis-oxazolidin-2-ones, we describe in this work the synthesis of *N*,*N*′-acylsulfonamide bis-oxazolidin-2-ones **3**, starting from simple and readily

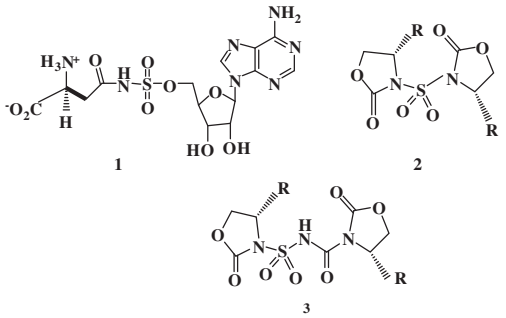


Figure 1. Substituted acylsulfonamides and bis-oxazolidinones sulfone.

available precursors. The use of amino acids allows the introduction of a chiral center in C-4 position (Fig. 1).

RESULTS AND DISCUSSION

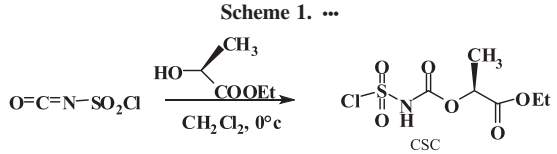
N-acylsulfonamides can be obtained by acylation of sulfonamides. Usually, acylation can be accomplished by the reaction of sulfonamides with acids, anhydrides, esters, or acid chlorides. Various synthetic procedures have been reported for the preparation of sulfonamides from acids using coupling reagents such as carbodiimides 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and *N,N'*-carbonyldiimidazole (CDI) [13].

The chlorosulfonyl isocyanate (CSI) was used to introduce the acylsulfonamide moiety on modified oxazolidinones [14] and is like a suitable reagent allowing the introduction of sulfonamide moieties in biomolecules [15].

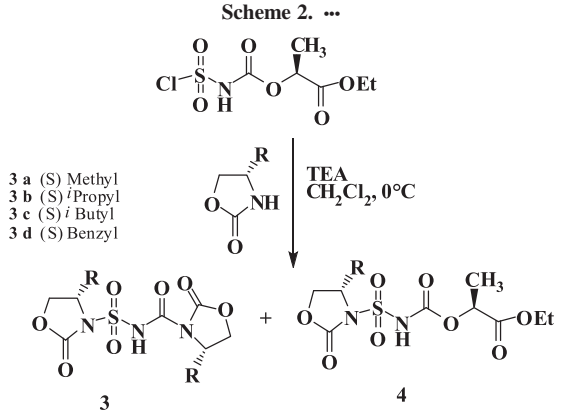
Our choice for (L)-ethyl lactate resides in the possibility of a selective intramolecular cyclization and introduces chirality (Scheme 1). Reaction of (L)-ethyl lactate with CSI in the presence of an excess of TEA gave the corresponding electrophilic *N*-chlorosulfonyl carbamate (CSC) [16].

At first, we performed an experiment with CSC and oxazolidin-2-ones, aiming to obtain the bis-oxazolidin-2-one heterocycles containing a sulfonyl bridge obtained by intramolecular cyclization (Scheme 3). Commercially available or easily accessible chiral oxazolidinon-2-ones react with CSC to give a mixture of **4a–d** and **3a–d** (Scheme 2). The mixture was easily separated by column chromatography eluted with dichloromethane to obtain four new derivatives of *N*-acylsulfonamide, ethyl (2*S*)-methyl-3-({[(4*R*)-4-(alkyl or benzyl)-2-oxo-1,3oxazolidin-3-yl]sulfonyl}amino)-3-oxopropanoate **4a–d** with 14–17% yields, and four new derivatives *N,N'*-acylsulfonamide bis-oxazolidin-2-ones, (4*S*)-4-methyl-*N*-{[(4*S*)-4-(alkyl

Scheme 1. ...



Scheme 2. ...



or benzyl)-2-oxo-1,3-oxazolidin-3-yl]sulfonyl}2-oxo-1,3- oxazolidine-3-carboxamide **3a–d** with 38–46% yields. However, the product **5** was not obtained, *in situ*, according to a mechanism proposed in Scheme 3.

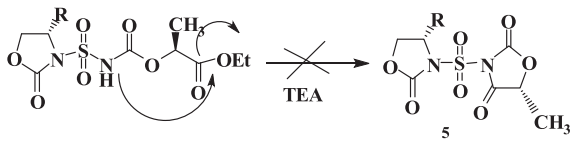
To confirm this hypothesis, we tried the cyclization of the product **4** alone with an excess of TEA with different operating conditions (solvent, temperature, and base) (Scheme 3); unfortunately, the reaction failed.

To confirm the proposed mechanism, we conducted an experiment with **4** and different chiral oxazolidin-2-ones (Scheme 4). From the reaction mixture, we isolated the compounds **3** with 75–82% yields.

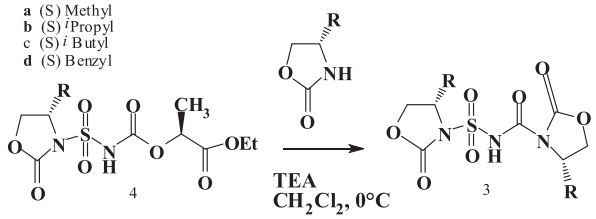
We found that ethyl lactate behaves as an activated ester. In this case, by addition of α-hydroxylester, the isocyanate gave the corresponding *N*-chlorosulfonyl-carbamate. In a second step, the carbamate reacts with two oxazolidin-2-ones, and the ethyl lactate moiety is easily cleaved under basic conditions. Concerning a possible mechanism, we assume that the lactate group serves as an activator and is easily removable in a second step.

The structures of all compounds were unambiguously confirmed by usual spectroscopic methods. For resulting

Scheme 3. ...



Scheme 4. ...



compounds **3a–3d**, spectra showed bands at 1785–1800 cm^{-1} and 1700–1705 cm^{-1}. ^{1}H-NMR spectra showed double doublet and multiplet systems due to the diastereotopic methylene protons of heterocycles and singlets corresponding to NH. The disappearance of the CO ester bond and the ethyl signal in NMR confirm the removal of the lactate fragment.

In conclusion, we have developed a rapid and convenient synthesis of different acylsulfonamide oxazolidin-2-one derivatives directly from commercially available reagents. Moreover, the reactivity of compounds **3** and **4** toward different electrophiles is currently in progress and will be reported in due course.

BIOLOGICAL ASSAYS

The *in vitro* cytotoxicity of the new agents **3b** and **3d** has been evaluated against the virulent strain RH of *Toxoplasma gondii*, to determine the inhibitory concentrations (IC_{50}) of each drug. We also evaluate the viability and the proliferation ability of human lymphocytes after drug treatment.

Parasite sensitivity assay. The activity of the new sulfamides on *T. gondii* was compared with that of sulfadiazine used as control (Fig. 2). *In vitro* studies were performed with MRC-5 fibroblast tissue cultures (BioMérieux, Marcy l'Etoile, France), with quantifications of *Toxoplasma* growth based on the number of trophozoites counted in the culture medium.

The RH strain tachyzoites were obtained from the peritoneal fluid of infected Swiss mice and purified as previously described [17].

Parasites in antibiotic-free Dulbecco's modified Eagle's medium (BioMérieux) were then added (10^4 parasites/mL) to human fibroblast cell line MRC-5. The incubation time required by the parasites to penetrate the MRC-5 cells is 4 h; increasing molecular concentrations (0.37, 0.75, 1.5, 2, 3, and 4 μg/mL) of the sulfamides dissolved in acetone 0.2% are then added in the cell culture. After 72 h, the tachyzoites were collected from the culture's supernatant and then counted in a Malassez cell. Viability of the parasites was assayed by trypan blue assay.

The effect of drugs on parasite survival was expressed as a percentage of cell viability relative to untreated cells, and IC_{50} were obtained from cytotoxicity curves (Fig. 3). The results demonstrated that for both **3b** and **3d** molecules, the inhibition was complete for concentrations over 4 μg/mL. The 50% (IC_{50}) of **3b** and **3d** was estimated to be respectively 1.5 and 3 μg/mL.

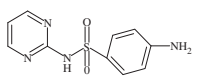


Figure 2. Structure of sulfadiazine.

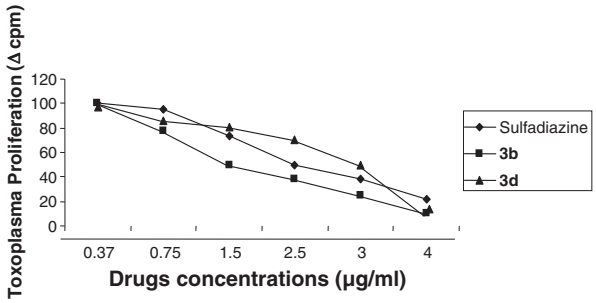


Figure 3. Drug concentrations at which the multiplication of *Toxoplasma gondii* is inhibited.

Thus, the IC_{50} of the two molecules were quite similar to that of the control one (2 μg/mL). The microscopic observation showed that there was no cytopathogenic effect on parasites and MRC-5 cells at the IC_{50}. No parasiticidal effect was seen on the parasites.

Controls conducted on both untreated and treated *Toxoplasma* with the solvent (acetone 0.2%) did not show any differences.

Lymphocyte sensitivity assay. The cytotoxicity of both drugs was evaluated by lymphocyte proliferation assay. In each well of a sterile U-bottom micro-culture plate, 100 μL of antibiotic-free culture medium (Dulbecco's modified Eagle's medium) was introduced, containing 2×10^5 lymphocytes. A total volume of 200 μL is then obtained by adding 100 μL of each drug (**3b** and **3d**), dissolved in acetone 0.2%, with final drug concentrations of 0.37, 0.75, 1.5, 2, 3, and 4 μg/mL. Phytohemagglutinine mitogen was used as control of cell proliferation at a concentration of 10 μg/mL. Cultures were maintained at 37°C in a humidified atmosphere of 5% CO_2 for 5 days. Sixteen hours before harvesting, 1 μCi of (^{3}H) methylthymidine (Amersham) was added. The radioactivity incorporated by the DNA was determined by liquid scintillation counting (Skatron AS, Norway).

All the tests were carried out in triplicate, and data were expressed in counts per minute (Δcpm) ± standard deviation. Controls included untreated and treated lymphocytes with the solvent (acetone 0.2%). Sulfadiazine was used as control.

Microscopic results showed absence of differences between treated and untreated lymphocytes, whether by the number of live cells or by staining. Cells were confluent, and the cytological aspect was normal. The inhibitory effect of the studied sulfamides on lymphocytes (Fig. 4) increases from a concentration estimated at 2 and 3 μg/mL respectively for both **3b** and **3d** molecules. Nevertheless, a cytopathogenic effect has been observed for the **3d** molecule at a specific concentration of 4 μg/mL (75% of cells died). The **3b** molecule seems to be less cytotoxic than the **3d** one.

In conclusion, our results suggest that the molecules have a dose-dependent immunomodulation activity and a

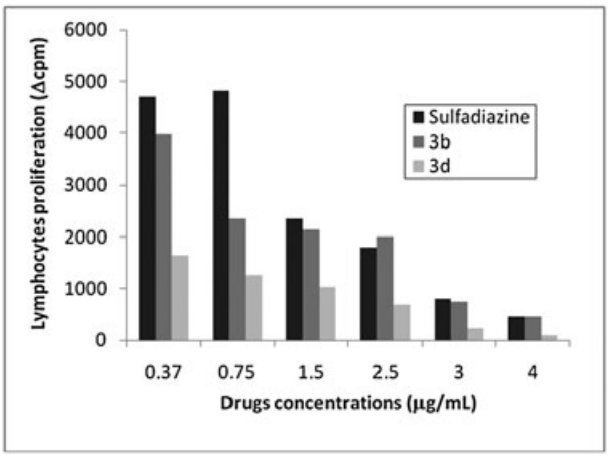


Figure 4. Lymphocyte proliferation responsiveness after stimulation with **3b** and **3d** sulfamides.

low cytotoxic effects on the studied cells. However, the **3b** molecule was less cytotoxic and highly active against *T. gondii* in cell cultures. Studies conducted *in vivo* would certainly help to better evaluate the cytotoxicity of these molecules on parasites by studying either mortality or histopathology values.

EXPERIMENTAL

All commercial chemicals and solvents were used as received. All reactions were carried out under an inert atmosphere of argon. TLC analyses were performed on silica gel $60F_{254}$ plates Merck, Art 1.05554, KGaA Darmstadt, Germany. Melting points were determined on a Büchi melting point 510 and are uncorrected. ^{1}H NMR spectra were recorded on a Brüker AC-250 (250 MHz) spectrometer using TMS as an internal standard, chemical shifts are expressed in δ (ppm) downfield from TMS, and coupling constants (*J*) are expressed in Hertz. Electron ionization mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ.

General procedure. To a solution of CSI (1.62 g, 11.4 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0°C was added dropwise 1 equiv of (L)-ethyl lactate (1.34 g, 11.4 mmol) in CH_2Cl_2 (5 mL). After 30 min, the carbamate formed was added to a solution of oxazolidin-2-one (2.01 g, 11.4 mmol), in presence of TEA (1.1 equiv) at 0°C. The mixture was stirred magnetically, and the progress of the reaction was monitored by TLC. In most cases, the reaction completed within 1 h. The reaction mixture was washed with 0.1*N* HCl and water, and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with CH_2Cl_2 to give 17% of carboxylsulfamides and 46% of *N*-acylsulfonamide bis-oxazolidin-2-one as a white solid.

Ethyl (2S)-2-methyl-2-({[(4R)-4-methyl-2-oxo-1,3-oxazolidin-3-sulfonyl}amino)carbonyl)oxy)ethanoate 4a. Yield: 15%, mp 127–129°C, R_f = 0,72 (CH_2Cl_2–MeOH, 9/1). $[\alpha]_D = -11.5$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 8.1 (s, 1H), 4.1 (d, *J* = 6.2 Hz, 3H), 4.2 (m, 1H), 4.2–4.0 (m, 2H), 3.75 (q, *J* = 6.5 Hz, 2H), 1.6 (d, *J* = 6.2 Hz, 3H), 1.5 (d, *J* = 6.3 Hz, 3H), 1.1 (t, *J* = 6.2 Hz, 3H).^{13}C NMR ($CDCl_3$, δ ppm): 170.2, 160.3, 154.5, 67.8, 67.4 62.3, 33.4, 19.2, 18.1, 15.4. IR (KBr, γ cm^{-1}): 3220 (NH), 1785, 1705, 1735, (CO), 1175–1385 (SO_2). MS ESI$^+$ 30 eV *m/z*: 325 $[M+H]^+$. HRMS Calcd. for $C_{10}H_{16}O_8N_2S$. M = 324.3076.

Ethyl (2S)-2-methyl-2-({[(4R)-4-isopropyl-2-oxo-1,3-oxazolidin-3-sulfonyl}amino)carbonyl)oxy)ethanoate 4b. Yield: 17%, mp 118–120°C, R_f = 0.80 (CH_2Cl_2–MeOH, 9/1). $[\alpha]_D = +3.5$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 8.2 (s, 1H), 5.0 (q, *J* = 7.0 Hz, 1H), 4.2 (q, *J* = 6.2 Hz, 2H), 4.1–4.0 (ddd, *J* = 3.5,7.9, 8.1 Hz, 2H), 3.9 (m, 1H), 1.6 (d, *J* = 6.2 Hz, 3H), 1.40 (m, 1H), 1.15 (2d, *J* = 9 Hz, 6H), 1.1 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 169.1, 159.6, 151.6, 67.4, 62.5, 61.3, 44.9, 32.1, 19.3, 19.1 15.5, 14.1. IR (KBr, γ cm^{-1}): 3200 (NH), 1787, 1734, 1705 (CO), 1191–1398 (SO_2). MS ESI$^+$ 30 eV *m/z*: 353 $[M+H]^+$. HRMS Calcd for $C_{12}H_{20}O_8N_2S$. M = 352.3608.

Ethyl (2S)-2-methyl-2-({[(4R)-4-isobutyl-2-oxo-1,3-oxazolidin-3-sulfonyl}amino)carbonyl)oxy)ethanoate 4c. Yield: 14%, mp 90–92°C, R_f = 0.75 (CH_2Cl_2–MeOH, 9/1), $[\alpha]_D = +8.5$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 6.9 (s, 1H), 5.0 (q, *J* = 7.2 Hz, 1H), 4.6 (m, 1H), 4.2 (q, *J* = 6.4 Hz, 2H), 4.3–4.0 (2dd, *J* = 3.5, 7.9, 8.1 Hz, 2H), 2.0 (m, 1H), 1.6 (m, 2H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.3 (t, *J* = 6.3 Hz, 3H), 0.9 (2d, *J* = 9 Hz, 6H). ^{13}C NMR ($CDCl_3$, δ ppm): 172.2, 162.8, 151.6, 67.4, 65.5, 61.3, 43.9, 35.1, 25.2, 23.1, 23.2, 17, 14.6. IR (KBr, γ cm^{-1}): 3250 (NH), 1784, 1742, 1702 (CO), 1182–1386 (SO_2). MS ESI$^+$ 30 eV *m/z*: 367 $[M+H]^+$. HRMS Calcd for $C_{13}H_{22}O_8N_2S$. M = 366.3874.

Ethyl (2S)-2-methyl-2-({[(4R)-4-benzyl-2-oxo-1,3-oxazolidin-3-sulfonyl}amino)carbonyl)oxy)ethanoate 4d. Yield: 17%, mp 117–119°C, R_f = 0.61 (CH_2Cl_2–MeOH, 9/1); $[\alpha]_D = +4.2$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 7.6 (m, 5H), 6.5 (s, 1H), 4.80 (q, *J* = 7.3 Hz, 1H), 4.25–4.10 (2dd, *J* = 3.2, 3.40, 9.80, 2H), 3.90 (q, *J* = 6.5 Hz, 2H), 3.40–2.80 (ddd, *J* = 3.50, 9.80, 13.50, 2H), 1.2 (d, *J* = 7.3 Hz, 3H), 1.1 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ ppm): 167.10, 157.20, 151.80, 138.00, 129.00, 128.00, 125.00, 67.40, 63.50, 61.30, 41.90, 40.10, 17.30, 15.50. IR (KBr, γ cm^{-1}): 3150 (NH), 1781, 1745 and 1685 (CO), 1130–1340 (SO_2). MS ESI$^+$ 30 eV *m/z*: 401 $[M+H]^+$. HRMS Calcd for $C_{16}H_2O_8N_2S$. M = 382.2607.

Synthesis of *N,N′*-acylsulfonamide bis-oxazolidinones. To stirred solutions of oxazolidin-2-ones (2.01 g, 11.4 mmol) in anhydrous CH_2Cl_2 (20 mL) in the presence of 1.2 equiv of TEA (0.9 mL, 13.7 mmol) at room temperature was added 1 equiv of compound **4** in the same solvent (15 mL). The reaction mixtures were stirred for 2 h. The resulting reaction solutions were washed with 0.1*N* HCl and water. The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residues were purified by flash chromatography on silica gel (eluted with CH_2Cl_2/EP 9:1) to give corresponding *N,N′*-acylsulfonamide bis-oxazolidin-2-one as white solids.

(4S)-4-Methyl-N-{[(4S)-4-methyl-2-oxo-1,3-oxazolidin-3-yl] sulfonyl}-2-oxo-1,3-oxazolidine-3-carboxamide 3a. Yield: 62%, mp 145.6°C, R_f = 0.78 (CH_2Cl_2–MeOH, 9/1). $[\alpha]_D = -7.5$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 7.2 (s, 1H, –SO_2–NH–CO–), 4.5–4.2 (m, 4H, 2CH_2-cyc), 4.1 (m, 2H, *CH-cyc), 1.3 (d, *J* = 7.2 Hz, 6H, 2CH_3). ^{13}C NMR ($CDCl_3$, δ): 160, 152.6, 151.8, 68.2, 67.5, 37, 38.1 19.5, 19.2. IR (KBr, γ cm^{-1}): 3155–3031 (NH), 1769, 1720 (CO), 1120–1345 (SO_2). MS ESI$^+$ 30 eV *m/z*: 306 $[M-H]^+$. HRMS Calcd for $C_9H_{13}O_7N_3S$. M = 307.2804.

(4R)-4-isopropyl-N-{[(4R)-4-isopropyl-2-oxo-1,3-oxazo-lidin-3-yl]sulfonyl}-2-oxo-1,3-oxazolidine-3-carboxamide 3b. Yield: 62%, mp 145.6°C, R_f = 0,78 (CH_2Cl_2–MeOH, 9/1). $[\alpha]_D$ = +8.5 (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$,δ): 8.2 (s, 1H, –SO_2–NH–CO–), 4.4 (m, 2H, CH_2-cyc), 4.2 (m, 2H, CH_2-cyc), 4.1 (m, 1H, *CH), 4.0 (m, 1H, *CH), 1.1–0.9 (2d, *J* = 9.2 Hz, 12H, 4CH_3). ^{13}C NMR ($CDCl_3$, δ): 162, 150.6, 151.2, 63.1, 62.2, 58.2, 59.1, 32. 31.3, 19.2, 19.3, 18.9, 18.4. IR (KBr, γ cm^{-1}): 3200, 3080 NH, 1787, 1702, (CO), 1120–1345 (SO_2). MS ESI$^+$ 30 eV *m/z*: 362 $[M - H]^+$. HRMS Calcd for $C_{13}H_{21}O_7N_3S$. M = 363.3867.

(4S)-4-Isobutyl-N-[(4S)-4-isobutyl-2-oxo-1,3-oxazolidin-3-yl]-2-oxo-1,3-oxazolidine-3-carbonyl sulfonamide 3c. Yield: 70%, mp 144.9°C, R_f = 0.80 (CH_2Cl_2–MeOH, 9/1). $[\alpha]_D$ = −5.5 (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 6.2 (s, 1H, –SO_2–NH–CO–), 4.6–4.5 (m, 4H, CH_2-cyc), 4.4 (m, 1H, *CH), 4.2 (m, 1H, *CH), 2.2 (m, 2H, CHiBut), 1.7 (m, 4H, CH_2iBut), 0.92 (d, *J* = 8.8 Hz, 12H, 4CH_3). ^{13}C NMR ($CDCl_3$, δ): 162, 152.4, 151.7, 68.2, 67.1, 43.2, 42.2, 24.4, 24.1, 23.2, 23.1. IR (KBr, γ cm^{-1}): 3170, 3028 (NH), 1789, 1678 (CO), 1130–1335 (SO_2). MS ESI$^+$ 30 eV *m/z*: 414 $[M + Na]^+$. HRMS Calcd for $C_{15}H_{25}O_7N_3S$. M = 391.4399.

(4S)-4-Benzyl-N-[(4S)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-oxo-1,3-oxazolidine-3-carbonyl sulfonamide 3d. Yield: 80%, mp 147.2°C, R_f = 0.56 (CH_2Cl_2–MeOH, 9/1). $[\alpha]_D$ = +6.5 (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, δ): 9.1 (s, 1H, –SO_2–NH–CO–) 7.10–7.3 (m, 10H, H-Ar), 4.9 (m, 1H, *CH-cyc) 4.7 (m, 1H, *CH-cyc), 4.2 (m, 4H, 2 CH_2-cyc) 3.6 (2dd, *J* = 3.5, 9.8, 13.4 Hz, 2H, CH_2-Ph), 3.1(m, 2H, CH_2-Ph). ^{13}C NMR ($CDCl_3$, δ): 161, 152.3, 151.8, 134, 130, 128.8, 128.1, 128.0, 124, 65.6, 64.9, 54.1, 47.0 40.9, 40.2. IR (KBr, cm^{-1}): 3166–3045 (NH), 1769, 1702 (CO), 1170–1375 (SO_2). MS ESI$^+$ 30 eV *m/z*: 460 $[M + H]^+$. HRMS Calcd for $C_{21}H_{21}O_7N_3S$. M = 459.4723.

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