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ORIGINAL ARTICLE

Synthesis and antibacterial activity of novel *N*-acylsulfonamides

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Sulfonamide;
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Abstract A series of novel *N*-acylsulfonamide derivatives were synthesized and characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The *N*-acylsulfonamides were prepared in four steps (carbamoylation, sulfamoylation, deprotection and acylation) starting from chlorosulfonyl isocyanate. These compounds were evaluated in vitro as antimicrobial agents against representative strains of Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*, *Acinetobacter*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*).

1. Introduction

The *N*-acylsulfonamide functional groups are found within numerous marketed agents for a wide range of therapies. In recent years, molecules containing acylsulfonamides have also been investigated as HCV protease inhibitors, (Raboisson et al., 2009) CXCR2 antagonists (Winters et al., 2009) and aryl acylsulfamide structures have been disclosed in a number of pharmaceutical patents as potential therapeutic agents with wide ranging biological activities (Reitz et al., 2009). New *N*-acylsulfonamides were recently described such as **1**. These compounds exhibit potent antiproliferative activity in three human tumor cell lines (Hep G2, PC-3 and B16-F10) (Huanqiu et al., 2012). The macrocyclic indole-base **2** inhibitors of the HCV NS5b polymerase (Vendeville et al., 2012) targeting the finger loop domain led to the discovery of lead compounds exhibiting improved potency in cellular assays and superior pharmacokinetic profile.

The most practical methods for the synthesis of *N*-acylsulfonamides, involve the reaction of parent sulfonamide with acyl chlorides or anhydrides in basic conditions (Kondo et al., 2000, 1998; Ishizuka et al., 2000; Huang et al., 2006). Acylation of sulfonamides with concentrated H_2SO_4 in carboxylic acid anhydride as solvent (Morisawa et al., 1980) or in acetonitrile (Martin et al., 2003) is one of the less common reports mentioning this transformation under acidic conditions. Another approach utilizes palladium-catalyzed carbonylation of aryl and heteroaryl halides with sulfamides utilizing microwave irradiation and vials pre-pressurized with carbon monoxide gas (Roberts et al., 2010).

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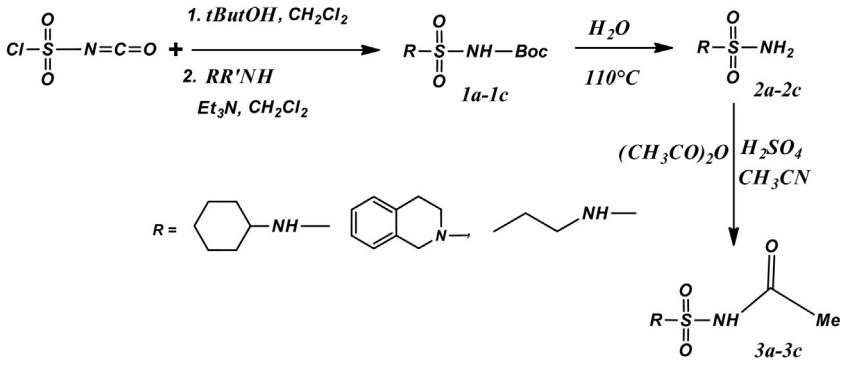

Scheme 1 Preparation of *N*-acylsulfonamides.

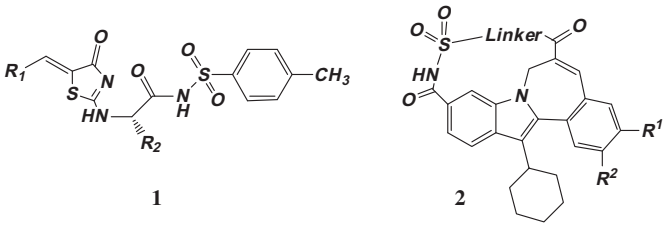

Figure 1 Examples of *N*-acylsulfonamide-containing drugs.

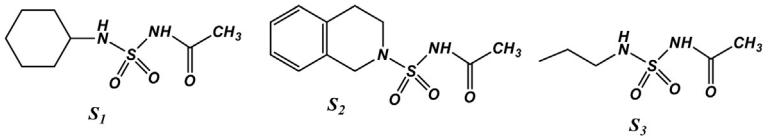

Figure 2 Structure of novel *N*-acylsulfonamides.

Herein, we report the synthesis of novel *N*-acylsulfonamides S_1, S_2, S_3 starting from chlorosulfonyl isocyanate by four steps carbamoylation, sulfamoylation, deprotection and acylation (Bouasla et al., 2011; Cheraiet et al., 2012). We have investigated the antibacterial activities of *N*-acylsulfonamides S1, S2 and S3 against Gram-positive *Staphylococcus aureus* ATCC25923 (b6), *S. aureus* isolate (b1), Gram-negative *Escherichia coli* ATCC25922 (b5), *E. coli* (clinical isolate) (b2), *Klebsiella pneumonia* (clinical isolate) (b4), *Pseudomonas aeruginosa ATCC 27853* (b7) and *Acinetobacter* (sp.) (clinical isolate) (b3) by both disk diffusion and minimal inhibition concentration (MIC) methods.

2. Chemistry

As part of the research for new derivatives of sulfonamides, we found that chlorosulfonyl isocyanate is a suitable reagent allowing the introduction of sulfonamide moiety in diverse molecules (Berredjem et al., 2003; Barbey et al., 2012; Bendjeddou et al., 2006; Khettache et al., 2006).

N-acylsulfonamides (Scheme 1) are prepared in four steps (carbamoylation, sulfamoylation, deprotection and acylation) by the reaction of chlorosulfonyl isocyanate (1 equiv.) and tertiobutanol (1 equiv.) in anhydrous CH_2Cl_2 (20 mL). After 30 min, the *N*-Chlorosulfonylcarbamate was added to a solution of primary or secondary amines (1 equiv.) in the same solvent (20 mL) in the presence of triethylamine (1.1 equiv.) at 0 °C. The resulting mixture was stirred for less than 2 h at room temperature. The reaction mixture was washed with HCl 0.1 N and water, the organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuum. The residue was purified by chromatography on silica gel (eluted with CH_2Cl_2) to give 85% of *N*-Boc sulfonamide as white solid.

The protected sulfonamides **1a–1c** refluxing in water for less than 15 min afforded deprotected sulfonamides **2a–2c** with quantitative yield. Preparation of *N*-acylsulfonamides **3a–3c**

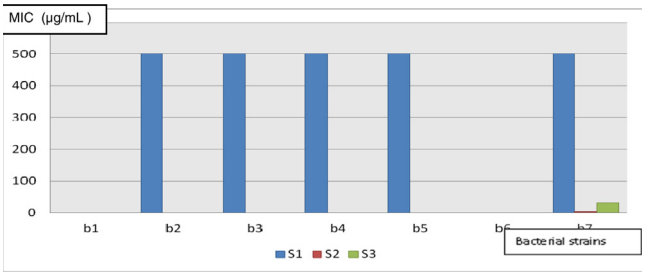

Figure 3 Results of the MIC of the various bacterial strains for the sulfonamides S1, S2 and S3.

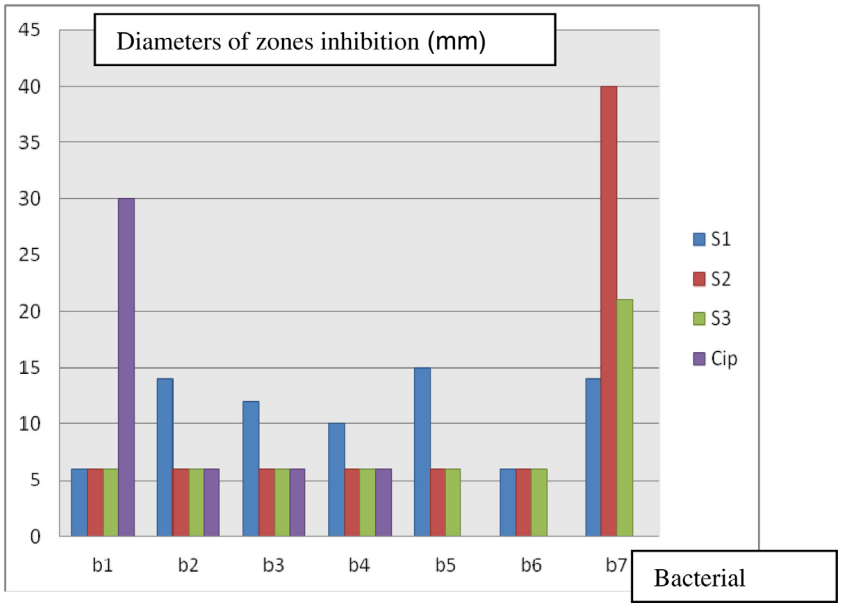

Figure 4 Diameters of zone inhibition of the bacterial strains with respective sulfonamides S1, S2, S3 and Cip.

was carried out by the reaction with obtained sulfonamides and acetic anhydride in acetonitrile in the presence of H_2SO_4 for 1 h.

3. *In vitro* antibacterial activity

During our study, the antibacterial activity of compounds was screened against various pathogens *in vitro* by using disk diffusion and micro dilution methods. Ciprofloxacin was used as control. The results of the synthesized compounds are shown in Figs. 1 and 2.

As seen in Figs. 1 and 2, S1 showed an antibacterial activity against all Gram negative referenced bacteria (*E. coli* ATCC25922 (b5), *P. aeruginosa ATCC 27853*(b7)) and clinical isolate (*E. coli* (b2), *K. pneumonia* (b4) and *Acinetobacter* (sp.) (b3)) at 500 μg/mL. The inhibitory diameters varied between 10 and 15 mm. All the clinical isolates used were resistant to ciprofloxacin.

S2 and S3 have higher diameters going to 40 mm for *P. aeruginosa* ATCC27853 (b7). Concentrations are 3.9 μg/mL and 31.25 μg/mL. respectively Figs. 3 and 4.

No activity was exhibited on *S. aureus*.

From the results obtained it comes out that no activity on the Gram positive bacteria was noted with our synthesized sulfonamides. On the contrary good activity was obtained on all the Gram negative bacteria used with S1.

The highest activity on *P. aeruginosa* (b7) was obtained with S2 at 3.9 μg/mL.

The solvent control did not show any antimicrobial activity.

4. Conclusion

In conclusion, we have developed a new and efficient route to *N*-acylsulfonamides. All compounds demonstrated an activity on clinical isolate and referenced Gram negative bacteria. Further research in this area is in progress. Consequently these synthesized compounds may be suggested for industrial applications.

5. Experimental section

5.1. General

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. Proton nuclear magnetic resonance was determined with a 360 WB or AC 250 MHz Bruker spectrometer using $CDCl_3$ and DMSO-d_6 as a 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), m (multiplet) and combination of these signals. Electron ionization mass spectra (30 eV) were recorded in positive mode on a Water MicroMass ZQ. All reactions were monitored by TLC on silica Merck h60 F254 (Art. 5554) percolated aluminum plates and were developed by spraying with ninhydrin solution.

Clinical isolates from parietal distal takings of patients' *S. aureus* (b1), *E. coli* (b2), *Acinetobacter* sp (b3) and *K. pneumonia* (b4) cultures were obtained from the laboratory of microbiology – CHU DORBAN.

We used, as control, three referenced strains: *S. aureus* ATCC 25923 (b6), *E. coli* ATCC 25922 (b5) and *P. aeruginosa* ATCC 27853(b7).

Minimal inhibitory concentrations (MIC) were determined by the micro dilution broth method following the National Committee for Clinical Laboratory Standard's procedures (Wayne, 1997a, 1997b). MIC are defined as the lowest concentrations 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 μg/mL of the compounds.

Inhibition zones of (*S1*), (*S2*) and (*S3*) were determined by the disk dilution method (Brunton et al., 2006). The culture suspensions were prepared and adjusted by comparing against 0.3 Mc Farland 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. 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. 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. Reference disk used for control is ciprofloxacin (Cip, 5 μg).

To insure 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.

5.2. General procedure for the synthesis of carboxylsulfonamide

A solution of tertiobutanol (2.27 g, 14.1 mmol) in anhydrous CH_2Cl_2 (10 ml) was added to a stirring solution of chlorosulfonyl isocyanate (CSI) (1.23 ml, 14.1 mmol) in (10 ml) of anhydrous CH_2Cl_2 at 0 °C dropwise over a period of 10 min. The resulting solution was transferred to a mixture of primary or secondary amine (1.87 g, 14.1 mmol) in CH_2Cl_2 (20 ml) in the presence of triethylamine (1.1 equiv). The solution was stirred at 0 °C for less than 1.5 h. The reaction mixture was washed with HCl 0.1 N and water, and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography to give carboxylsulfamides in good yields.

5.2.1. Tert-butyl (1-Cyclohexyl)amino sulfonylcarbamate (1a)

Yield: 90%, **mp** 109–110 °C, $\mathbf{R_f}$ = 0.90 (CH_2Cl_2/MeOH, 9/1), **^{1}H NMR** ($CDCl_3$, δ ppm): 1.05 (s, 9H, tBu), 1.65–2.1 (m, 10H, CH_2-cyc), 5.15 (d, 1H, J = 7.35, NH–CH-cyc), 7.18 (s, 1H, (NH-Boc). **IR** (KBr, γ en cm^{-1}): 1720.1 (C═O), 3420.5 and 3221.4 (2NH), 1367 and 1132 (SO_2). **SM** ESI$^+$ 30ev m/z: 279 $[M+H]^+$ 100%. HRMS calcd. for $\mathbf{C_{11}H_{22}N_2O_4S}$. M = 278.

5.2.2. Tert-butyl 3,4-dihydroisoquinolin-2(1H)-yl sulfonylcarbamate (1b)

Yield: 80%, **mp** 136–137 °C, $\mathbf{R_f}$ = 0.75 (CH_2Cl_2/MeOH, 9/1), **^{1}H NMR** ($CDCl_3$, δ ppm): 1.5 (s, 9H, tBu), 2.90 (t, J = 5.87 Hz, 2H, C**H$_2$**–Ph), 3.30 (t, J = 6.02 Hz, 2H, C**H$_2$**–N), 4.50 (s, 2H, Ph–C**H$_2$**–N), 7.1–7.6 (m, 4H, Ar–**H**), 7.8(s,1H, NH–Boc). **IR** (KBr, γ en cm^{-1}): 1725.2 (C═O), 3423.8 (NH), 1643.6 (C═C), 1364.2 and 1133 (SO_2). **SM** ESI$^+$ 30ev m/z: 313 $[M+H]^+$ 100%. HRMS calcd. for $\mathbf{C_{14}H_{20}N_2O_4S}$. M = 312.

5.2.3. Tert-butyl (1-Propyl) amino sulfonylcarbamate (1c)

Yield: 97%, **mp** 110–111 °C, $\mathbf{R_f}$ = 0.80 (CH_2Cl_2/MeOH, 9/1), **^{1}H NMR** ($CDCl_3$, δ ppm): 1.01(t, J = 5.02 Hz, 3H, CH_3), 1.60 (s, 9H, tBu), 1.65 (m, 2H, CH_3–CH_2), 3.2 (m, 2H, CH_2–NH),5.2(t, 1H, J = 6.04 Hz, CH_2–NH), 7.32 (s,1H, NH-Boc). **IR** (KBr, γ en cm^{-1}): 1710.5 (C═O), 3300.4 (NH), 1370 and 1150 (SO_2). **SM** ESI$^+$ 30ev m/z: 239 $[M+H]^+$ 100%. HRMS calcd. for $\mathbf{C_8H_{18}N_2O_4S}$. M = 238.

5.3. General procedure for the N-acylation of sulfonamide

The sulfonamides (1equiv.) were reacted with acetic anhydride (1.5 equiv.) in the presence of 0.3% of H_2SO_4 in acetonitrile at 80 °C. After 2 h the reaction mixture was evaporated, diluted with dichloromethane and washed with water. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude compounds were purified by column chromatography (CH_2Cl_2/MeOH, 9/1) to afford the corresponding acyl sulfonamides in a good yield.

5.3.1. N-(1–cyclohexyl)amino sulfonyl acétamide (3a)

Yield: 87%, **mp** 197–198 °C, $\mathbf{R_f}$ = 0.52 (CH_2Cl_2/MeOH, 9/1), **^{1}H NMR** ($CDCl_3$, δ ppm): 1.65–2.1 (m, 10H, CH_2-cyc), 5.15 (d, 1H, J = 7.35, NH–CH_2 cycle), 2.0 (s, 3H, CH_3). **IR** (KBr, γ en cm^{-1}): 3372 and 3265 (2NH), 1730 (C═O), 1360 and 1153 (SO_2). **SM** ESI$^+$ 30ev *m/z*: 221 $[M+H]^+$ 100%.HRMS calcd. for $\mathbf{C_8H_{16}N_2O_3S}$. M = 220.

5.3.2. N-(3,4-dihydroisoquinolin-2(1H)-yl sulfonyl) acetamide (3b)

Yield: 65%, **mp** 172–173 °C, $\mathbf{R_f}$ = 0.38 (CH_2Cl_2/MeOH, 9/1), **^{1}H NMR** ($CDCl_3$, δ ppm): 8.1 (s, 1H, N**H**), 7.2–7.0 (m, 4H, **H**-Ar), 4.5 (s, 2H, ph-C**H$_2$**N), 3.7 (t, 2H,J = 5.7 Hz, C**H$_2$**N), 2.9 (t, 2H, J = 5.8 Hz, 2H, C**H$_2$**-ph), 2.1 (s, 3H, C**H$_3$**). **^{13}C NMR** (CDCl3, δ ppm): 173, 134.1, 127.5, 126.9, 126.3, 125.7, 48.1, 47.2, 25.3, 21.6. **IR** (KBr, γ en cm^{-1}): 3260 (NH), 1711 (C═O), 1361 and 1155 (SO_2). **SM** ESI$^+$ 30ev *m/z*: 255 $[M+H]^+$ 100%. HRMS calcd. for $\mathbf{C_{11}H_{14}N_2O_3S}$. M = 254.

5.3.3. N-(1–propyl) amino[sulfonyl acétamide (3c)

Yield: 79%, **mp** 167–168 °C, $\mathbf{R_f}$ = 0.42 (CH_2Cl_2/MeOH, 9/1), **^{1}H NMR** ($CDCl_3$, δ ppm): 1.01 (t, J = 5.02 Hz, 3H, CH_3), 1.65 (m, 2H, CH_3–CH_2), 3.2 (m, 2H, CH_2–NH), 5.2 (t, 1H, J = 6.23 Hz, CH_2–NH), 2.1 (s, 3H, CH_3). **IR** (KBr, γ en-cm^{-1}): 3370 and 3263 (2NH), 1721 (C═O), 1380 and 1154 (SO_2). **SM** ESI$^+$ 30ev *m/z*: 181 $[M+H]^+$ 100%. HRMS calcd. for $\mathbf{C_5H_{12}N_2O_3S}$. M = 180.

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