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EFFICIENT SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL CYCLIC SULFAMIDES

Sihem Hessainia[1], Fouzia Bouchareb[1], Hadjer Cheloufi[1], Malika Berredjem[1,*], Hajira Berredjem[2], Imen Becheker[2] and Nour-Eddine Aouf[1]

[1]Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Sciences Faculty, Chemistry Department Badji-Mokhtar, Annaba University, BP 12, 23000, Algeria.
[2]Laboratory of Cell Toxicology, General Direction of Scientific Research and Technological Development, Algeria.
* E-mail: malika.berredjem@univ-annaba.org

ABSTRACT

A series of modified acyclic sulfamides and cyclic sulfamides were synthesized efficiently, using sulfuryl chloride that is the suitable available reagent allowing the introduction a sulfamide moiety. The cyclosulfamides were prepared in two steps (duplication and cyclization) starting from a primary amines. These compounds were preliminarily tested for antibacterial activity against Gram-positive and Gram-negative bacteria. The synthesized compounds exhibited excellent antibacterial activity as compared to the standard sulfamide drug, especially against the clinical strains.

Keywords: sulfamides, cyclosulfamides, antibacterial activity.

INTRODUCTION

The sulfamides are an important class of nitrogen containing compounds owing to their efficiently used in pharmaceutical chemistry. In the last decade, they have been used as precursor to develop biologically active compounds[1]. Further, it has been found that these compounds show promising applications in the field of medicinal chemistry[2-5]. In the point of view, cyclic sulfamides are used as potential inhibitors of proteolytic enzymes[6], human leukocyte elastase **I**[7-8], serine protease[9], inhibitors of noroviruses **II**[10], as 11β-hydroxysteroid dehydrogenase 1 inhibitors (11β6HSD1) [11] and potential carbonic anhydrase isoenzymes inhibitors [12].There are various synthetic methodologies for the preparation of sulfamides and cyclosulfamides [13-21]. From these methods, the most common one is the one which involve nucleophilic attack of ammonia, primary or secondary amines to sulfonyl chloride in the presence of a base.

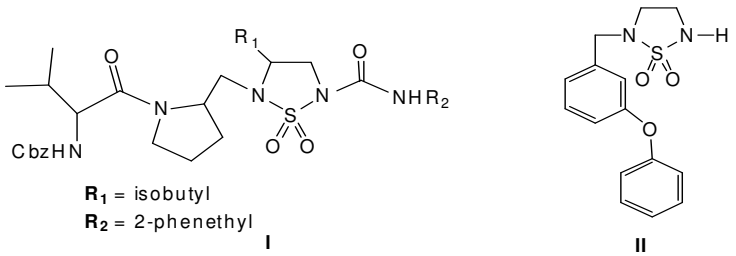


Fig.-1: Some cyclic sulfamide drugs

EXPERIMENTAL

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. High-resolution mass were measured on a Joel SX 102 mass spectrometer. All reactions were monitored by TLC on silica Merck h60 F254 (Art. 5554) percolated aluminium plates and were developed by spraying with ninhydrin solution.

Typical procedure for the preparation of *N, N'*-bis-(alkyl) sulfamides

To a stirred solution of primary amine (1 eq, 1 g, 9.34 mmoL) in anhydrous dichloromethane, triethylamine (2.5 eq, 3.25 mL, 9.34 mmoL) was added drop wise at 0 °C. After 15 min, SO_2Cl_2 (0.5 eq, 0.37 mL, 9.34 mmoL) was added slowly over 45 min and the resulting yellow solution was then warmed at room temperature over 3 h. The mixture was diluted with 100 ml of CH_2Cl_2 and acidified with HCl (0.1 N, 10 mL). The organic layer was washed with water (40 mL), dried over anhydrous sodium sulfate and concentrated in vacuum. Recrystallization of the crude product in ether afforded pure expected *N, N'*-bis-(alkyl) sulfamides **1a-f** as white solids.

***N, N'*- Bis (benzyl) sulfamide, 1a**

White solid, yield 69 %. R_f = 0.42 (CH_2Cl_2 / MeOH). mp: 182 - 183 °C. ^{1}H NMR (250 MHz, DMSO-d_6, δ ppm): 4.0 (d, *J* = 4.02 Hz, 2 H, CH_2), 7.22 - 7.31 (m, 10 H, H-Ar), 7.43 (t, *J* = 7,46 Hz, 2 H, NH). ^{13}CNMR (250 MHz, $CDCl_3$, δ ppm): 45.83 (CH_2), 127.06, 127.75, 128.26 and 138.40 (C-Ar).

***N, N'*- Bis (propyl) sulfamide, 1b**

White solid, yield 66 %. R_f = 0.46 (CH_2Cl_2 / MeOH). mp: 110 - 111 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm) : 0.9 (t, *J* = 7.35 Hz, 6 H, C**H$_3$**), 1.6 (m, 4 H, C**H$_2$**-CH_3), 3.0 (t, *J* = 7.11 Hz, 4 H, C**H$_2$**-N), 4.25 (s, 2 H, N**H**). ^{13}C NMR (250 MHz, $CDCl_3$, δ ppm): 11.2 (**C**H_3), 21.9 (**C**H_2-CH_3), 42.8 (**C**H_2-NH).

***N, N'*- Bis (phenylethyl) sulfamide, 1c**

White solid, yield 70 %. R_f = 0.64 (CH_2Cl_2 / MeOH). mp: 80 - 82 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 1.5 (d, *J* = 6.51 Hz, 6 H, C**H$_3$**), 4.5 (m, 4 H, ***C**H **+** N**H**), 7.15 (m, 4 H, **H**$_{ortho}$-Ar), 7.25 (m, 6 H, (4**H**$_{meta}$-Ar, 2**H**$_{para}$-Ar)). ^{13}C NMR (250 MHz, $CDCl_3$, δ ppm): 20.0 (**C**H_3), 47.0 (***C**H), 126.7, 126.9, 128.5 and 143.0 (**C-**Ar). IR (KBr, *v* cm^{-1}): 1149.5 - 1315.4 (SO_2), 1450.4 (C=C_{Ar}), 3309.6 (NH).

***N, N'*- Bis (cyclohexyl) sulfamide, 1d**

White solid, yield 50 %. R_f = 0.33 (CH_2Cl_2 / MeOH). mp: 148 - 150 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 1.25 (m, 8 H, C**H$_2$**cyc), 1.5 (m, 4 H, C**H$_2$**cyc), 1.75 (m, 4 H, C**H**cyc), 2.00 (m, 4 H, C**H**cyc), 3.25 (s, 2H, C**H**cyc-N), 4.25 (s, 2H, N**H**). ^{13}C NMR (250 MHz, $CDCl_3$, δ ppm): 24.8 (**C**H_2 Hexane), 25.0 (**C**H_2 Hexane), 32.0 (**C**H_2 Hexane), 43.0 (**C**H Hexane). IR (KBr, *v* cm^{-1}): 1141.8 - 1442.7 (SO_2), 2858.3 - 2935.5(C-H_{ali}), 3282.6 (NH).

***N, N'*-Bis (3-bromopropyl) sulfamide, 1e**

White solid, yield 90 %. R_f = 0.57 (CH_2Cl_2 / MeOH). mp: 89 - 91 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 2.15 (m, 4 H, C**H$_2$**CH_2Br), 3.25 (q, *J* = 6.48 Hz, 4 H, C**H$_2$**N), 3.5 (t, *J* = 6.24 Hz, 4 H, C**H$_2$**Br), 4.53 (t, *J* = 6.11 Hz, 2 H, N**H**). ^{13}C NMR (250 MHz, $CDCl_3$, δ ppm): 30.36 (**C**$H_2$$CH_2$Br), 31.99 (**C**$H_2$N), 41.37 (**C**$H_2$Br). IR (KBr, *v* cm^{-1}): 1137.9 - 1311 (SO_2), 3440.8 (NH). MS ESI$^+$ 30eV m / z: 338.89 $[M+1]^+$, 75%.

***N, N'*- Bis (2-chloroethyl) sulfamide, 1 f**

White solid, yield 85 %. R_f = 0.44 (CH_2Cl_2 / MeOH). mp: 80 - 82 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 3.50 (q, *J* = 5.76, 4 H, C**H$_2$**NH), 3.75 (t, *J* = 5.54 Hz, 4 H, C**H$_2$**Cl), 4.80 (t, *J* = 5.92 Hz, 2 H, N**H**). ^{13}CNMR (250 MHz, $CDCl_3$, δ ppm): 41.3 (**C**H_2NH), 43.0 (**C**H_2Cl). IR (KBr, *v* cm^{-1}): 1137.9 - 1315.4 (SO_2), 3436.9 (NH). MS ESI$^+$ 30eV m / z: 222.09 $[M+1]^+$, 65%.

General procedure for inter cyclization
To a solution of *N, N'*-bis-(alkyl) sulfamides **1a-d** (1 eq, 0.5 g, 1.81 mmoL) in dry acetone (3mL) and 10eq (2.5 g, 1.81 mmoL) of K_2CO_3, was added drop wise a large excess of 1, 2-dibromoethane (10 eq, 1.56 mL, 1.81 mmoL). The reaction mixture was refluxed for 3h and monitored by TLC. The residue was filtered and concentrated under vacuum. The products were purified by column chromatography on silica gel (CH_2Cl_2) to give **2a-d** in 60-65 % yields.

***N, N'*-Dibenzyl-1, 2, 5-thiadiazolidine 1, 1-dioxide, 2a**
White solid, yield 61 %. R_f = 0.46 (CH_2Cl_2). mp: 63-65 °C. ^{1}H NMR (250MHz, DMSO-d_6, δ ppm): 3.14 (s, 4H, C**H$_2$**cyc), 4.23 (s, 4 H, C**H$_2$**Ph), 7.25-7.40 (m, 10 H, **H**-Ar). ^{13}CNMR (250MHz, $CDCl_3$, δ ppm): 44.9 (**C**H_2Ph), 51.6 (**C**H_2cyc), 128.2, 128.8, 128.9 and 135.1 (**C-**Ar).

***N, N'*-Dipropyl-1, 2, 5-thiadiazolidine 1, 1-dioxide, 2b**
Yellow oil, yield 64 %. R_f = 0.40 (CH_2Cl_2). ^{1}H NMR (250MHz, $CDCl_3$, δ ppm): 0.98 (t, 6 H, C**H$_3$**), 1.65 (m, 4 H, C**H$_2$**CH_3), 2.95 (t, *J* = 2.98 Hz, 4 H, C**H$_2$**N), 3.28 (s, 4 H, C**H$_2$**cyc). ^{13}CNMR (250MHz, $CDCl_3$, δ ppm): 11.4 (**C**H_3), 21.2 (**C**H_2CH_3), 45.6 (**C**H_2N), 49.6 (**C**H_2cyc).

***N, N'*-bis(1-phenylethyl)-1, 2, 5-thiadiazolidine 1, 1-dioxide, 2c**
White solid, yield 65 %. R_f = 0.31 (CH_2Cl_2). mp: 146 - 148 °C. ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 1.58 (d, *J* = 1.62 Hz, 6H, C**H$_3$**), 2.86 (m, 4 H, C**H$_2$**cyc), 4.45 (q, 4 H, *C**H**), 7.25 - 7.46 (m, 10 H, **H**-Ar). ^{13}CNMR (250 MHz, $CDCl_3$, δ ppm): 19.9 (**C**H_3), 43.2(**C**H_2cyc), 57.5 (***C**H), 127.4, 128.2, 128.8 and 140.7 (**C-**Ar).

***N, N'*-dicyclohexyl-1, 2, 5-thiadiazolidine 1, 1-dioxide, 2d**
Yellow oil, yield 60 %. R_f = 0.41 (CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 1.20 (m, 8 H, C**H$_2$**cyc), 1.35 (m, 4 H, C**H**cyc), 1.48 (m, 4 H, C**H$_2$**cyc), 1.60 (m, 4 H, C**H**cyc), 2.50 (m, 2 H, C**H**cyc-N), 2.67 (s, 4 H, C**H$_2$**cyc). ^{13}CNMR (250MHz, $CDCl_3$, δ ppm): 25 (**C**H_2 Hexane), 25.4 (**C**H_2 Hexane), 30 (**C**H_2 Hexane), 50.5 (**C**H_2cyc) 51.1 (**C**H Hexane).

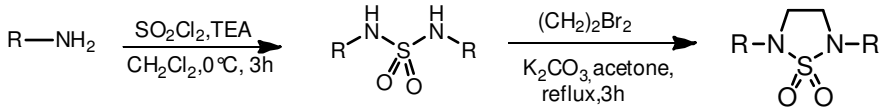
General procedure for intra cyclization
A mixture of *N, N'*-bis-alkyl sulfamides **1e-f** (1 eq, 0.5g, 1.48 mmoL) in 5ml of acetone and 3eq (0.61 g, 1.48 mmoL) of K_2CO_3 was stirred at room temperature for 3h. The reaction was monitored by TLC then the reaction mixture was filtered and concentrated under vacuum. The products were purified by column chromatography on silica gel (CH_2Cl_2) to give **2e - f** in 70 - 80 % yields.

***N*-(3-bromopropyl)-1, 2, 6-thiadiazinane 1, 1-dioxide, 2e**
Yellow oil, yield 80 %. R_f = 0.47 (CH_2Cl_2 / MeOH). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 1.75 (m, 2 H, CH_2C**H$_2$**.cycCH_2), 2.15 (m, 2 H, C**H$_2$**CH_2Br), 3.20 (t, *J* = 6.59 Hz, 2 H, C**H$_2$**cycN), 3.40 (t, *J* = 5.66 Hz, 2 H, C**H**$_2$cyc NH), 3.50 (t, *J* = 6.4 Hz, 4 H, C**H$_2$**Br + C**H$_2$**N), 4.50 (s, 1H, N**H**).^{13}C NMR (250 MHz, $CDCl_3$, δ ppm): 21.3 (NHCH_2**C**H_2cyc CH_2 N), 29.2 (**C**H_2CH_2Br), 31.0 (**C**H_2Br), 46.5 (**C**H_2N), 43.1 (**C**H_2cyc NH), 49.0 (**C**H_2cyc N). MS ESI$^+$ 30eV m / z: 257.7 $[M+1]^+$, 100%.

***N*-(2-chloroethyl)-1, 2, 5-thiadiazolidine 1, 1-dioxide, 2f**
Yellow oil, yield 72 %. R_f = 0.44 (CH_2Cl_2 / MeOH). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 3.45 (q, *J* = 6.70 Hz, 2 H, C**H$_2$**.cycNH), 3.55 (m, 4 H, C**H$_2$**.cycN + C**H$_2$**N), 3.75 (t, *J* = 6.30 Hz, 2 H, C**H$_2$**Cl), 4.30 (t, *J* = 6.70 Hz, 1 H, N**H**). ^{13}C NMR (250 MHz, $CDCl_3$, δ ppm): 40.0 (**C**H_2Cl), 45.2 (**C**H_2cyc NH), 45.4 (**C**H_2CH_2Cl), 51.0 (**C**H_2cyc N), IR (CCl_4, *v* cm^{-1}): 1150 - 1355 (SO_2), 3298 (NH). MS ESI$^+$ 30eV m / z: 185.3 $[M+1]^+$, 100%.

RESULTS AND DISCUSSION

We prepared a series of symmetric linear sulfamides **1a-f** starting from a primary amine by application of the Dannek and Dougerty methods1[9, 21]. The symmetric cyclic sulfamides **2a-d** was prepared in two steps (duplication-cyclization) by the reaction of primary amine and sulfuryl chloride in the presence of triethylamine, the reaction was monitored by TLC. These compounds were produced in good yield (Scheme-1), as white crystalline solid after usual acid base work-up and column chromatography. The intermolecular cyclization of compounds **1a-d** was easily achieved by using dibromoethane in the presence of potassium carbonate in acetone. The heterocyclic compounds **2a-d** were obtained as white powder or yellow oil in (60-65 %) yields.

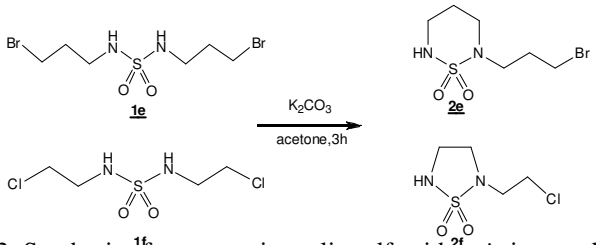


R: 1a:Bn
1b:Pr
1c:PhCH(Me)
1d:C_6H_{11}
1e:Br(Pr)
1f:Cl(Et)

R: 2a:Bn
2b:Pr
2c:PhCH(Me)
2d:C_6H_{11}

Scheme-1: Procedure synthesis of symmetric cyclic sulfamides.

The asymmetric cyclic sulfamides **2e-f** can be prepared easily in good yield (75-85%) by treatment of linear sulfamides **1e-f** with potassium carbonate (K_2CO_3) in a dry acetone at room temperature (Scheme-2).



Scheme-2: Synthesis of asymmetric cyclic sulfamides *via* intramolecular cyclization.

Antibacterial activity

We carried out *in vitro* an antibacterial evaluation of sulfamides **1a**, **1b** and **1c** and cyclic sulfamides **2a**, **2b** and **2c**, against clinical strains isolated from patients presenting urinary infections. The inhibition zone area was evaluated by the diffusion method on solid medium Mueller Hinton; the MICs were determined on a liquid medium.

Table-1: Antibacterial activities of 1a-c

Compounds / Strains	1a			1b			1c		
	C (µg / ml)	IZ (mm)	MIC (µg / ml)	C (µg / ml)	IZ (mm)	MIC (µg / ml)	C (µg / ml)	IZ (mm)	MIC (µg / ml)
E. c. ATCC 25922[a]	64 8 2	12 20 12	2	512 128	13 17	128	64 32	15 14	32
E. c. 1[b]	512 128 64	23 13 15	64	512 256 128	10 13 14	128	128 4	18 20	4

E. c. 2[c]	512 128 64	20 14 16	64	512 256 128	14 16 20	128	256 128 8	17 19 21	8
S. a. ATCC 25923[d]	64 8 2	12 10 16	2	265 16 8	17 16 12	16	512 128 4	18 15 16	4
S. a. 1[e]	512 128	13 14	128	64 32	14 16	64	512 64 32	20 16 13	64
S. a. 2[f]	512 128	14 15	128	64 32 16	16 18 20	64	512 128 64	18 16 14	128

C : Compound concentrations for zone inhibitions
IZ : Diameters of zones inhibition
MIC : Minimum Inhibitory Concentration
[a] *Escherichia coli* ATCC 25922.
[b] *Escherichia coli* 1.
[c] *Escherichia coli* 2.
[d] *Staphylococcus aureus* ATCC 25923.
[e] *Staphylococcus aureus* 1.
[f] *Staphylococcus aureus* 2.

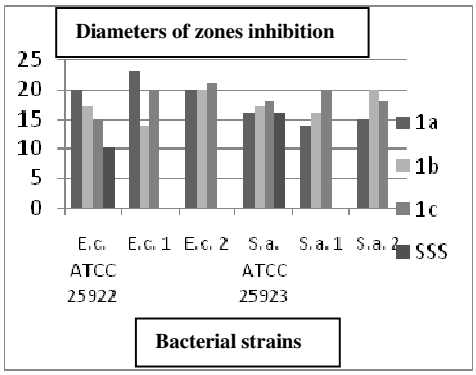


Fig.-2: Diameters of zone inhibition of the bacterial strains with respectively 1a, 1b and 1c.

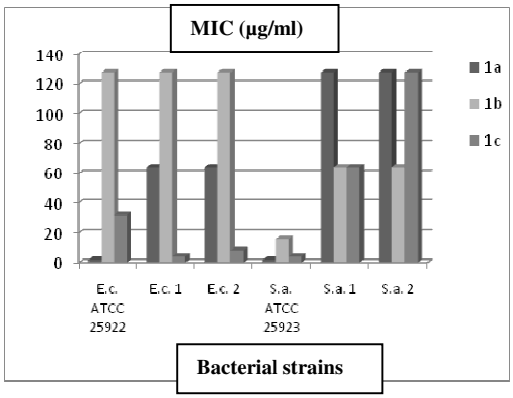


Fig.-3: Results of the MIC of the tested bacterial strains for the 1a, 1b and 1c.

1a, **1b** and **1c** gave remarkable zones of inhibition varying between 14 mm and 23 mm (Fig.-2). These results showed a good activity of the new compounds against the clinical strains as compared to the control sulfamides (sulphonamide, Bio Rad). In fact, all clinical strains were resistant to the control drug.

Escherichia coli strains showed a low value of MIC with **1c** (32 and 8 µg / ml); with **1b** the MIC was the same for the three strains: 128 µg / mL; **1a** showed an interesting MIC for the reference strain (2µg / mL); the value for the two clinical strains was 64 µg / mL. The reference strain *Staphylococcus aureus* showed the weakest MIC value between 2 and 16 µg /mL for the 3 molecules; for the clinical strains we obtained the same MIC (64 µg / mL) for the **1b** molecule. For **1a**, the MIC value is 128 µg / mL; the **1c** molecule showed a MIC between 64 µg / mL for strain 1 and 128 µg / mL for strain 2 (Fig.-3).

Table-2: Antibacterial activities of 2a-c

compounds / Strains	1a			1b			1c		
	C (µg / mL)	IZ (mm)	MIC (µg / mL)	C (µg / mL)	IZ (mm)	MIC (µg / mL)	C (µg / mL)	IZ (mm)	MIC (µg / mL)
E. c. ATCC 25922[a]	16 8	15 17	16	Resistant			Resistant		
E. c. 1[b]	16 2	14 16	2	512 256 128	16 18 15	128	64 16 8	22 18 16	16
E. c. 2[c]	64 32	15 17	32	512 128	17 16	128	32 16	20 18	16
S. a. ATCC 25923[d]	64 32	14 13	64	64 32	16 13	64	64 16	16 12	64
S. a. 1[e]	Resistant			Resistant			64 32	14 12	64
S. a. 2[f]	512 256	13 15	256	512 256	14 16	256	32 16	16 14	32

C : Compound concentrations for zone inhibitions
IZ : Diameters of zones inhibition
MIC : Minimum Inhibitory Concentration
[a] *Escherichia coli* ATCC 25922.
[b] *Escherichia coli* 1.
[c] *Escherichia coli* 2.
[d] *Staphylococcus aureus* ATCC 25923.
[e] *Staphylococcus aureus* 1.
[f] *Staphylococcus aureus* 2.

The molecules gave interesting zones of inhibition varying between 22 mm for the clinical strains *Escherichia coli* 1 with **2c** at a concentration of 64 µg / ml, and 12 mm for the clinical strains of *Staphylococcus aureus* 1 and 2 with the same molecule. Therefore, we observed a resistance either of the reference strain *Escherichia coli* ATCC 25922 to **2b** and **2c**, or the clinical strain of *Staphylococcus aureus* 1 to **2a** and **2b** (Fig.-4).

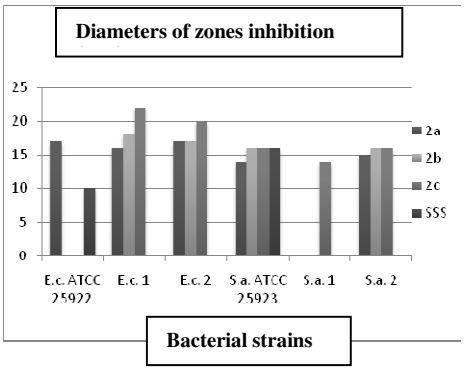


Fig.- 4: Diameters of zone inhibition of the bacterial strains with respectively 2a, 2b and 2c.

Most of the new compounds have a good activity against the clinical strains as compared to the control sulfamide (sulphonamide, Bio Rad) which was inactive against all clinical strains.
The MIC value of **2a, 2b** and **2c** molecules is between 2 and 256 µg / mL. For **2a**, the MIC is between 2 and 256 µg / mL, for **2b** the MIC is between 64 and 256 µg / mL and for **2c** the MIC is between 16 and 64 µg / mL (Fig.-5).

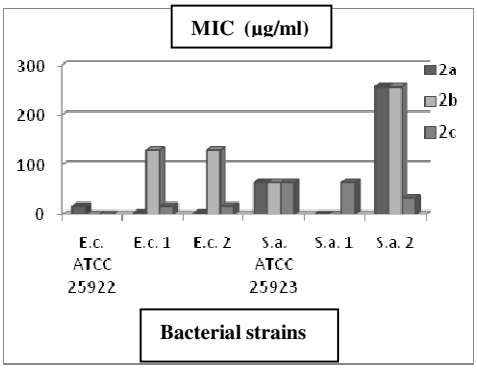


Fig.-5: Results of the MIC of the various bacterial strains for the 2a, 2b and 2c.

CONCLUSION

In conclusion, the synthesis of novel cyclic sulfamides was achieved in two steps: **1**. Duplication; free amines (benzylamine, propylamine, ethylphenylamine, cyclohexylamine, bromopropylamine and chloroethylamine) were reacted with sulfuryl chloride in the presence of Et_3N. **2**. Cyclization; the synthesized sulfamides were reacted with 1, 2-dibromoethane in the presence of K_2CO_3. In addition, the antibacterial activity of the synthesized compounds **1a-c** and **2a-c** has been evaluated. The biological results showed that the clinical strains and the control strains were sensitive to the different concentrations of both newly synthesized compounds. Therefore, from these findings it can be conclude that these molecules present a significant antibacterial activity on gram positive and gram negative strains. Better results were obtained with compounds 1a-c than 2a-c ones. Furthermore, compound 1c gave better activity with lower MICs than the other compounds for both *Escherichia coli* and *Staphylococcus aureus.*

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