Research Article

The Antibacterial and Cytotoxic Activities of Four New Sulfonamides Against Clinical Gram-Negative Bacteria

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ABSTRACT

A series of four substituted sulfonamide derivatives **1a-d** were evaluated, *in vitro*, for the antibacterial and cytotoxic activities against 216 clinical Gram-negative bacteria, and three reference strains: *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603 and *P. aeruginosa* ATCC 27853. The antibacterial effect of synthesized compounds was investigated by using the disk diffusion method to evaluate the inhibition zones. The MIC values were determined by the dilution broth method; the MIC_{50} and MIC_{90} were calculated. The cytotoxic properties of the tested compounds were carried out, *in vitro*, by the brine shrimp bioassay. The results showed that the tested compounds have significant antibacterial activity against the clinical isolates, excepted *S. odorifera* and *C. freundii*. No antibacterial activity was shown whith the sulfonamide **1a** against the clinical isolates. Only the sulfonamide **1a** showed a significant cytotoxicity to the brine shrimp nauplii with LC50 equal to 18,29 µg/ml. It may be concluded that promising innovative compounds **1b-d,** with high antibacterial activity and no toxicity effect, could be exploited against resistant pathogens.

Keywords: Antibacterial activity, Cytotoxicity, Gram-negative bacteria, Sulfonamides, MIC.

INTRODUCTION

The abuse of antibiotics has, unfortunately, led to the emergence of drug resistant strains which have a significant impact on the patient's morbidity and mortality.[1,2] Indeed, the past decade, we have seen a significant increase of the infections with multidrug-resistance especially in Gram-negative bacteria, which are of major global concern given limited therapeutic options, untoward clinical outcomes, and excess costs of care.[3,4] In some cases, the formerly effective antimicrobial agents are no longer useful.[1] Thus, antibiotic resistance has become a major public health problem in the world.[4] Even though the arsenal of antibacterial molecules available is considerable, it cannot solve all these problems.[5] Therefore, a clear need is required for the development of innovative antimicrobial agents with better pharmacological profiles.

Sulfonamides are among the most widely used antibacterial agents in the world. They were the first effective chemotherapeutic agents used systematically for the prevention and cure of bacterial infections in humans and some animals, mainly because of their low cost, low toxicity and excellent activity against bacterial diseases.[6]

Many sulfonamide derivatives were synthesized, characterized and tested for many biological activities such as antibacterial[7], anti-tumour[8], diuretic[9,10] and hypoglycemic properties.[11] Screening of their toxicity is crucial to guarantee the safety of the users.[12]

For new drug discovery research, brine shrimp lethality assay was considered as an important, convenient and cheap tool for preliminary assessment of cytotoxicity.[13,14]

The *in vivo* lethality in a simple zoological organism (brine shrimp) was developed by Meyer[15] and might be used as a simple tool to guide screening of physiologically active compounds, where one of the simplest biological responses to monitor is lethality, since there is only one criterion: either dead or alive.[14,16]

The present study was carried out to investigate the *in vitro* antibacterial activity against clinical Gram-negative bacteria and the cytotoxic effect on brine shrimp of four innovative sulfonamide derivatives.

MATERIALS AND METHODS

Bacterial Isolates

A total of 216 clinical Gram-negative bacteria were used in this study. The isolates collected from public and private sanitary establishments were mainly isolated from different samples: urine, pus, blood, and protected distal sampling (PDS).

The identification of the bacterial isolates was made on cultural and biochemical characters (API 20E system and APINE system, BioMérieux, France).

The reference strains were used as a control (Pasteur Institute, Algiers).

Tested Compounds

The sulfonamide derivatives used in this study, were obtained in three steps from a simple and efficient methodology. The carboxylsulfamides were prepared by an efficient method,[17,18] implying the reaction of the tert-butanol and chlorosulfonyl isocyanate in anhydrous methylene chloride at 0°C. After 30 min the N-chlorosulfonyl carbamate and triethylamine were added

to a solution of primary amine in the same solvent. After completion of the reaction, the reaction mixture was washed with HCl 0.1 N and then with water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo, to give carboxylsulfamides as a white powder in excellent yields.

The deprotection reaction of the obtained compounds was carried out in distilled water at 100°C for 30–60 min to give sulfonamides **1a-d** with quantitative yields. The structure of all compounds was confirmed by usual spectroscopic methods: 1H NMR, 13C NMR, mass spectrometry and IR.[19]

The sulfonamides **1a-d** (Table 1) were solubilized in acetone and then serial dilutions were made in a concentration range from 0,5 to 512 µg/ml.

Two commercial drugs were used as positive controls and were diluted in the same manner: Control 1: Bactrim, sulfamethoxazole-trimethoprime (400/80mg) (Laboratoire Roche, France), and control 2: Sulfaguanidine (500 mg) (Merck, France).

Antibacterial Bioassay

Determination of the Inhibition Zones

The newly synthesized compounds **1a-d** were screened for antibacterial activity against reference strains and clinical Gram-negative isolates. The inhibition zones were performed with the disk diffusion method.[20] The antimicrobial screening was assessed using Mueller–Hinton agar that was poured into each sterile Petri dishes, allowed to solidify and finally seeded with a bacterial inoculum with an OD_{625} about 0,08. Empty sterilized disks of 6 mm (Schleicher and Schule, Germany) were placed on agar plates; each one was impregnated with 20 µl of the different concentrations of the compounds. The cultures were incubated at 37°C for 24 hrs. Inhibition zones formed on the medium were measured in millimeter (mm).

The standard drugs, control 1 and 2, were used as positive controls. All tests were performed in duplicate, and experiment was repeated three times.

Determination of the Minimal Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) values of sulfonamide derivatives **1a-d** were determined by the dilution broth method following the procedures recommended by the CLSI.[20]

All tests were performed in Mueller–Hinton broth. Bacterial inoculum with an OD_{625} about 0.08 was added to each tube containing tested compound at geometric dilutions ranging from 0,5 to 512 µg/ml; a control tube without sulfonamide was used. The tubes were incubated at 37°C for 24 hrs. The results were recorded according to the presence or absence of bacteria growth comparatively to the controls. As previously, control 1 and 2 were used as positive controls. Two replicates were done for each compound, and experiment was repeated three times.

MIC50 and MIC90 Calculation

The concentration of each antimicrobial agent, that inhibited 50% (MIC 50) and 90% (MIC 90) of the strains, was calculated for each of the sulfonamide compounds singly. The formula of geometric means was used as follows: [21,22]

$$MIC_{50} = (M<50) + \frac{(n-X)\times[(M>50)-(M<50)]}{Y}$$

M < 50: MIC of the highest cumulative percentage below 50%.

M > 50: MIC of the lowest cumulative percentage above 50%.

n: 50% of the number of organisms tested.

X: number of organisms in the group at M <50.

Y: number of organism in the group at M >50.

Determination of the Minimal Bactericidal Concentration (MBC)

The minimal bactericidal concentration (MBC) was carried out to assess the compounds concentration that can kill or inhibit the growth of the tested organisms. Absence of growth was interpreted as bactericidal action while growth represented a bacteriostatic action.[20] The MBC was established on nutritive agar by sub-culturing 0,1 ml of tubes showing no turbidity at MIC concentration of the tested sulfonamide derivatives, at 37°C for 24 hrs.

Cytotoxic Bioassay

Hatching the Shrimp

All the synthesized compounds were screened for their cytotoxicity (brine shrimp bioassay) using the protocol of Meyer.[15] Brine shrimp (*Artemia salina*) eggs were hatched in a shallow rectangular plastic dish (22 x 32 cm), filled with artificial seawater, which was prepared with commercial salt mixture and distilled water. An unequal partition was made in the plastic dish with the help of a perforated device. Approximately 50 mg of eggs were sprinkled into the large compartment, which was darkened while the minor compartment was illuminated. After 48 hrs, the phototropic nauplii were collected from the lighted side.

Bioassay

Ten nauplii were transferred to each vial containing 0,5 ml of the tested sulfonamide derivative and 4 ml of the artificial seawater (30 shrimps/dilution) then, the volume was adjusted with seawater to 5 ml per vial. A drop of dry yeast suspension (3 mg/5 ml artificial seawater) was added as food (nutrient source) for the nauplii of *A. salina*. After 24 hrs, the number of survivors was counted.

The LC50 (lethal concentration) of the tested sulfonamides was performed by Probit Analysis and linear

regression,[23] defined as the concentration of different compounds required that killed 50% of the tested population. Data was analyzed using the Prism5 software.

Statistical Analysis

Data analysis was performed using one-way analysis of variance (ANOVA) followed by *t* student test. All the results were expressed as mean ± S.E.M. (standard error of the mean). Statistical significance was considered at $P < 0,05$.

RESULTS AND DISCUSSION

The inhibition zones and the MIC for the reference strains

The results showed an interesting antibacterial activity of **1b-d** compounds; however, no antibacterial activity was observed with the compound **1a** against Gram-negative bacteria.

The diameters of the inhibition zones of the sulfonamide derivatives **1a-d** against the reference strains vary between 15 and 20 mm. The smaller diameter (15 mm) was obtained with *P. aeruginosa* ATCC 27853, the greater diameter (20 mm) was obtained with *K. pneumoniae* ATCC 700603 (Figure 1). The obtained MIC vary between 1 and 128 µg/ml (Figure 2).

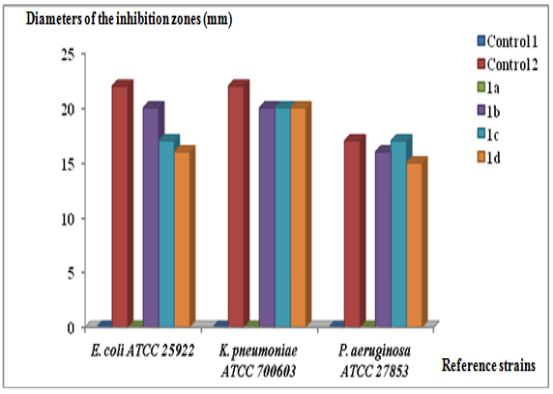


Figure 1: Diameters of the inhibition zones of the reference strains against the sulfonamide derivatives **1a-d.**

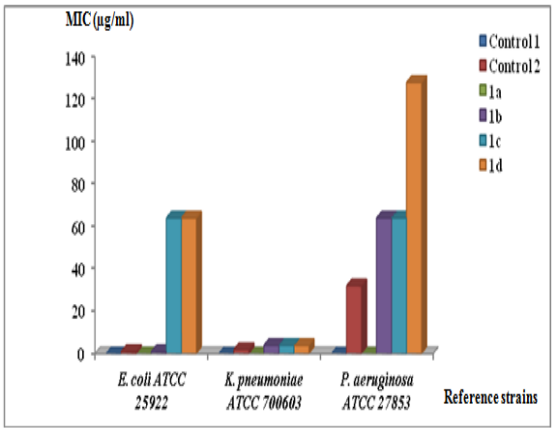


Figure 2: MIC of the reference strains against the sulfonamide derivatives **1a-d.**

Only the control 2 (Sulfaguanidine) was active against the tested reference strains.

An antibacterial activity with Gram-positive reference strain (*S. aureus* ATCC 25923) was obtained in a previous study with the four compounds **1a-d** including the compound **1a**.[24]

The Inhibition Zones of the Clinical Isolates

According to the results in Table 2, the *in vitro* evaluation of the antibacterial activity of the sulfonamide derivatives **1b-d** [N- (3-fluorophenyl) sulfonamide; N- (phenyl) sulfonamide and N- (phenylethyl) sulfamide] has highlighted an important dose-dependent antibacterial activity. The majority of clinical isolates demonstrated an interesting inhibition zones ranging from 17,16 ± 1,09 to 23,85 ± 1,06 mm; however, *S. fonticola* and *C. freundii* isolates were resistant to the four compounds.

The smaller diameters of inhibition zones were obtained with *E. coli, K. pneumoniae*, *K. oxytoca* and *P. aeruginosa* isolates varying between 17,00 ± 0,89 and 18,15 ± 1,25 mm (photos 1, 2); the highest diameters (23,2 ± 0,44 and 23,85 ± 1.06 mm) were obtained with *Salmonella sp*. and *A. baumannii* respectively with the sulfonamide **1d** (photos 3, 4).

In a previous study,[24] the **1a** compound [N- (4-methoxyphenyl) sulfonamide] has given antibacterial activity with Gram-positive bacteria (*S. aureus*) showing an inhibition zone diameters of 22,15 ± 6,22 mm.

Comparing these results to those obtained with the controls, we note that the Bactrim (Control 1) showed similar results to those obtained with the compounds **1b-d** for some bacterial species.

The majority of the tested strains showed resistance to the sulfaguanidine (Control 2) excepted *S. marcescens* and *Salmonella sp*.

Minimal Inhibitory Concentration MIC

Determination of the MIC, MIC_{50} and MIC_{90} of the synthesized compounds 1a-d for clinical Gram-negative fermentative bacteria

The results of the MIC, MIC_{50} and MIC_{90} of the sulfonamide derivatives **1a-d** for the clinical Gram-negative fermentative isolates are shown in Table 3.

The MIC was ranged between 16 and 512 µg/ml for **1b-c** sulfonamides.

The inhibition percentages vary between 54, 83 and 62,5%.

The MIC_{50}/MIC_{90} values corresponding to those of the MIC range showing a high sensitivity level of the new compounds.

E. coli, *K. pneumoniae* and *K. oxytoca* showed a significant resistance against the new sulfonamides **1b-d**.

For the other isolates, a significant antibacterial activity was obtained with a low MIC, ranged between 0,5 and 64 µg/ml.

S. marcescens and *Salmonella sp.* presented the best results with MIC ranging between 1- 8 µg/ml and 0,5 - 4 µg/ml respectively. The percentage of sensitivity was 100% for these isolates.

S. odorifera and *C. freundii* were resistant to new drugs as well as controls.

Determination of the MIC, MIC_{50} and MIC_{90} of the synthesized compounds 1a-d for the clinical Gram-negative non fermentative bacteria

The Gram-negative non fermentative bacteria (Table 4), *P. aeruginosa* and *A. baumannii* had different sensitivities against the tested compounds. *P. aeruginosa* showed MIC ranged between 32 and 512 µg/ml with percentages of inhibition that vary between 50 and 57, 81%.

A. baumannii was the most sensitive strain; MIC were low and vary between 0, 5 and 2 µg/ml. The percentage of inhibition was 100%.

The Minimal Bactericidal Concentration MBC

The bacterial count determined a number greater than 10^2 UFC/ml in all Petri dishes, which corresponding to 0.01% of the initially number of bacteria. According to these results, the synthesized compounds **1b-d** were bacteriostatic.

The *in vitro* evaluation of the antibacterial activity of the sulfonamide derivatives **1a-d** has highlighted an important antibacterial activity. The presence of electron donating and withdrawing groups, size and shape of molecule, might be influencing the selective antibacterial activity.[19] Aromatic fluorine substituent improves bioavailability and increases potency. It was therefore concluded that the presence of fluor moiety, in addition to phenyl group, was found to be essential for its high antibacterial activity.[19,24] Kumar[25] indicated that the presence of phenyl ring attached to the sulfonamide moiety increased the antimicrobial potential of the synthesized compounds against the tested microbial strains; these results are coherent with our results.

Cytotoxic Bioassay

Cytotoxicity effect of the sulfonamide derivatives **1a-d** was carried out by the brine shrimp lethality assay method. From the data recorded in Table 5, it is evident that only the compound **1a** displayed potent cytotoxic activity against *Artemia salina* nauplii with LC50 equal to 18,29 µg/ml, while the other compounds **1b-d**, were not cytotoxic with LC50 equal to 29,63 ; 66,1 and 20,99 µg/ml respectively.

In this work, the sulfonamide **1a** (N-(4-methoxyphenyl) sulfamide**)** showed a significant lethality against the brine shrimp. The toxicity of the molecule **1a** is due to the presence of the methoxy group. Indeed, structure-activity relationships (SAR) revealed that cytotoxicity increased with the increase in the number of methylene groups such as the methoxy, which has been demonstrated by Chohan.[26]

Claffey[27] investigated the synthesis and cytotoxicity of the methoxy phenyl substituted titanocenes, and demonstrated that the titanocenes showed an increased cytotoxicity in comparison to unsubstituted titanocene dichloride. They had also established that the number and the positioning of methoxy groups on the phenyl ring involved the activity and the cytotoxicity of the compounds.

This cytotoxic activity relationship may help to serve as a basis for future direction towards the development of cytotoxic agents for clinical applications such as the screening of the antitumour effect of the **1a** compound guided by the simple Brine shrimp lethality biological test.

Table 1: Chemical structure of the sulfonamide derivatives **1a-d.**

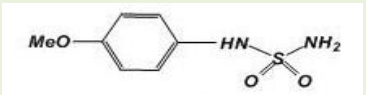
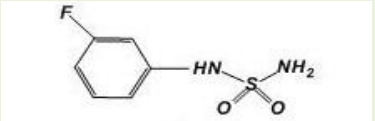
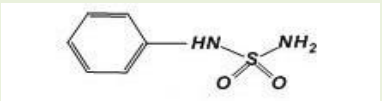
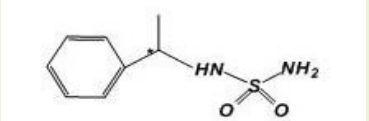
Tested Sulfonamides	Nomenclature	Molecular Formulas	MW (g/mol)	Chemical Structures
1a	N-(4-methoxyphenyl) sulfamide	$C_7H_{10}N_2O_3S$	203	
1b	N-(3-fluorophenyl) sulfamide	$C_6H_7N_2O_2SF$	190	
1c	N-(phenyl) sulfamide	$C_6H_8N_2O_2S$	172	
1d	N-(phenylethyl) sulfamide	$C_8H_{12}N_2O_2S$	200	

Table 2: Diameters of inhibition zones of the clinical isolates against the sulfonamide derivatives **1a-d**.

Clinical isolates	Diameter of inhibition zones (mm) means ± DS					
	1a	1b	1c	1d	Control 1	Control 2
E. coli	R	17,30 ± 0,92	17,16 ± 1,09	18,15 ± 1,25	26,41 ± 2,27	R
K. pneumoniae	R	17,35 ± 0,86	17,58 ± 1,00	17,70 ± 1,04	17,33 ± 1,03	R
K. oxytoca	R	17,00 ± 0,89	17,60 ± 0,54	17,60 ± 1,14	21,83 ± 4,02	R
P. mirabilis	R	21,36 ± 1,21	19,84 ± 0,89	19,94 ± 1,22	R	R
P. vulgaris	R	18,80 ± 1,22	19,60 ± 0,69	19,50 ± 0,97	19,20 ± 0,83	R
E. cloacae	R	18,10 ± 1,10	18,90 ± 0,73	18,00 ± 1,15	21,20 ± 5,21	R
E. aerogenes	R	20,00 ± 0,00	19,66 ± 0,57	19,33 ± 0,57	21,00 ± 1,00	R
S. marcescens	R	20,20 ± 0,83	19,60 ± 0,54	20,00 ± 0,70	23,00 ± 1,00	19,00 ± 1,00
S. fonticola	R	19,00 ± 0,00	20,00 ± 0,00	19,00 ± 0,00	26,00 ± 0,00	R
S. odorifera	R	R	R	R	R	R
Salmonella sp.	R	23,20 ± 0,44	20,40 ± 0,54	20,20 ± 0,44	22,60 ± 0,54	26,20 ± 0,83
C. freundii	R	R	R	R	22,66 ± 1,15	R
P. aeruginosa	R	17,62 ± 1,31	17,51 ± 1,26	17,43 ± 1,23	17,23 ± 1,53	R
A. baumannii	R	23,85 ± 1,06	21,52 ± 0,87	21,85 ± 1,06	22,08 ± 6,93	R

R: Resistant; **SD:** Standard Deviation

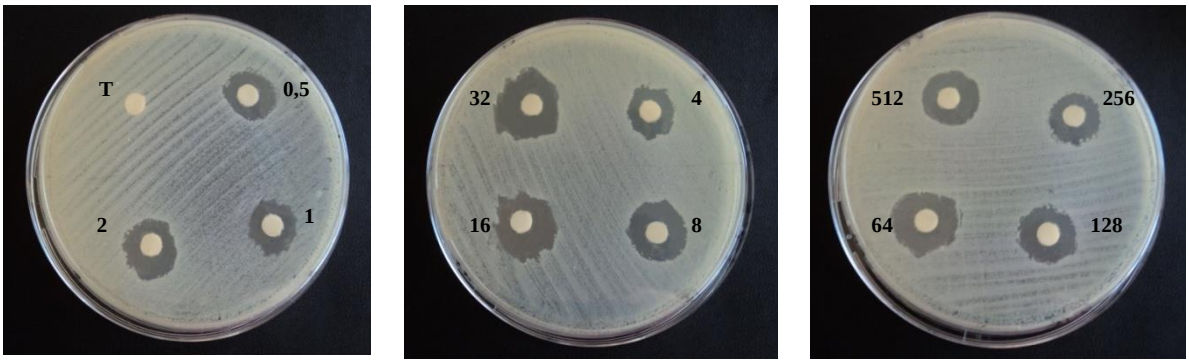


Photo 1: Inhibition zones of *E. coli* at different concentrations (µg/ml) of the sulfonamide **1b**.

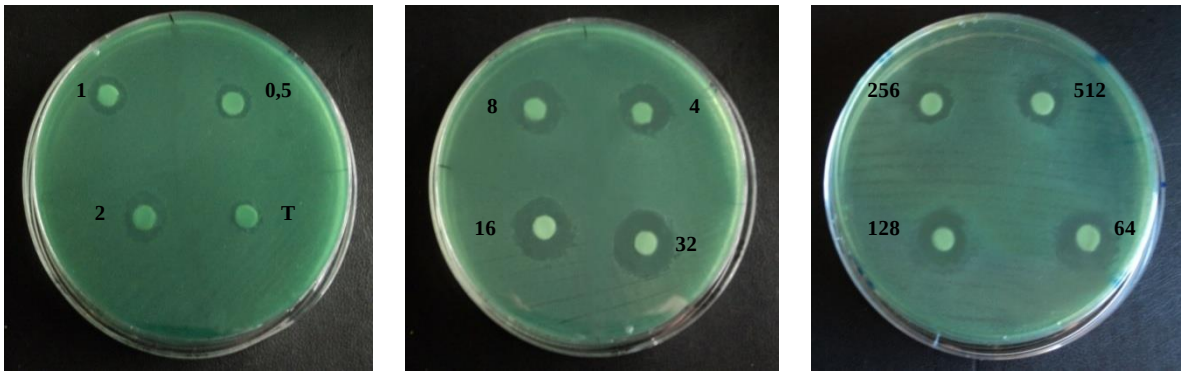


Photo 2: Inhibition zones of *P. aeruginosa* at different concentrations (µg/ml) of the sulfonamide **1c**.

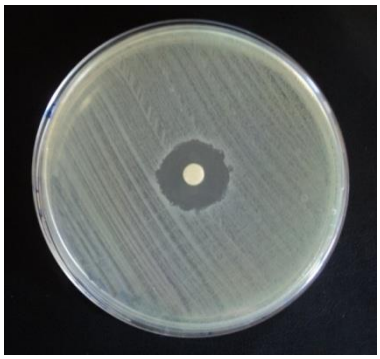


Photo 3: Diameter of the inhibition zone of *Salmonella sp.* (20 mm) by sulfonamide **1d** (16 µg/ml).

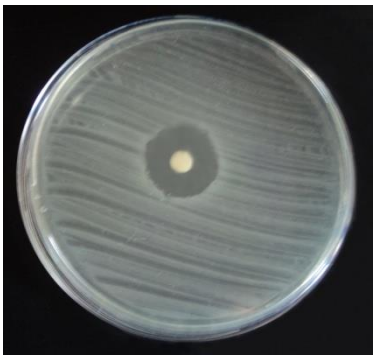


Photo 4: Diameter of the inhibition zone of A. baumannii (22 mm) by sulfonamide 1c (1 µg/ml).

Table 3: Values of the MIC, MIC_{50} and MIC_{90} of the sulfonamide derivatives **1a-d** for the clinical Gram-negative fermentative isolates

Clinical isolates	Tested Compounds	MIC (µg/ml)			Inhibition (%)
		Range	MIC_{50}	MIC_{90}	
E. coli	1a	R	R	R	0
	1b	32-256	80	256	62,5
	1c	32-512	256	416	56,25
	1d	32-512	28,57	> 512	59,37
	Control 1	0,5-2	0,8	2	37,5
	Control 2	R	R	R	0
K. pneumoniae	1a	R	R	R	0
	1b	32-512	108,8	277,33	54,83
	1c	32-512	44	> 512	54,83
	1d	32-512	48	320	54,83
	Control 1	8-16	ND	12,1	18,75
	Control 2	R	R	R	0
K.oxytoca	1a	R	R	R	0
	1b	32-128	48	96	60
	1c	32-64	40	ND	50
	1d	16-128	28	48	50
	Control 1	2-16	7	12,5	60
	Control 2	R	R	R	0
P. mirabilis	1a	R	R	R	0
	1b	1-8	1,75	10	100
	1c	1-8	3,28	5,66	100
	1d	1-16	3,75	30	100
	Control 1	R	R	R	0
	Control 2	R	R	R	0
P. vulgaris	1a	R	R	R	0
	1b	4-64	7	96	100
	1c	2-16	3	24	100
	1d	2-16	3,33	28	100
	Control 1	4-8	ND	ND	50
	Control 2	R	R	R	0
E. cloacae	1a	R	R	R	0
	1b	16-64	25,6	ND	100
	1c	16-32	ND	ND	100
	1d	16-64	28	40	100
	Control 1	0,5-4	3,5	3,75	50
	Control 2	R	R	R	0
E. aerogenes	1a	R	R	R	0
	1b	8	ND	4	100
	1c	8-16	ND	4	100
	1d	4-16	6	12	100
	Control 1	2-4	2,5	2,5	100
	Control 2	R	R	R	0
S. marcescens	1a	R	R	R	0
	1b	1-2	ND	ND	100
	1c	1-4	1,75	2,5	100
	1d	1-4	1,75	2,5	100
	Control 1	4-8	ND	ND	100
	Control 2	R	R	R	0
S. fonticola	1a	R	R	R	0
	1b	8	ND	ND	100
	1c	4	ND	ND	100
	1d	8	ND	ND	100
	Control 1	8	ND	ND	100
	Control 2	R	R	R	0

S. odorifera	1a	R	R	R	0
	1b	R	R	R	0
	1c	R	R	R	0
	1d	R	R	R	0
	Control 1	R	R	R	0
	Control 2	R	R	R	0
Salmonella sp.	1a	R	R	R	0
	1b	0,5-2	ND	2,5	100
	1c	1-2	1,16	ND	100
	1d	1-4	1,75	2,5	100
	Control 1	1-4	1	1,25	100
	Control 2	0,5-2	1	1,25	100
C. freundii	1a	R	R	R	0
	1b	R	R	R	0
	1c	R	R	R	0
	1d	R	R	R	0
	Control 1	2-4	ND	ND	100
	Control 2	R	R	R	0

R: Resistant; **ND:** Not Determined

Table 4: Values of the MIC, MIC_{50} and MIC_{90} of the sulfonamide derivatives **1a-d** for the clinical Gram-negative non fermentative isolates.

Clinical isolates	Tested Compounds	MIC (µg/ml)			Inhibition (%)
		Range	MIC_{50}	MIC_{90}	
P. aeruginosa	1a	R	R	R	0
	1b	32-256	60,44	277,33	50
	1c	32-512	148	> 512	54,68
	1d	32-512	165,33	> 512	57,81
	Témoin 1	8-64	20,62	43,5	20,31
	Témoin 2	128-256	128	155,3	10
A. baumannii	1a	R	R	R	0
	1b	0,5-2	ND	2,5	100
	1c	0,5-2	0,53	1,8	100
	1d	0,5-2	ND	2,5	100
	Témoin 1	0,5-8	3,5	7,5	57,14
	Témoin 2	R	R	R	0

R: Resistant; **ND:** Not Determined

Table 5: The cytotoxic effect of the sulfonamide derivatives **1a-d** against the Brine shrimp nauplii

Tested compounds	Concentrations (µg/ml)	Initial number of nauplii	Total death			Total survivors			Percentage mortality	LC_{50} (µg/ml)	Confidence Interval
1a	512	10	9	9	10	1	1	0	93,33	**18,29**	13,44 - 24,91
	256	10	10	9	9	0	1	1	93,33		
	128	10	9	9	10	1	1	0	93,33		
	64	10	8	8	7	2	2	3	76,66		
	32	10	8	7	8	2	3	2	76,66		
	16	10	5	6	6	3	4	4	56,66		
	8	10	0	0	0	10	10	10	0		
	4	10	0	0	0	10	10	10	0		
	2	10	0	1	0	10	9	10	3,33		
	1	10	0	0	0	10	10	10	0		
	0,5	10	0	0	0	10	10	10	0		
1b	512	10	10	10	10	0	0	0	100	**29,63**	25,58 - 34,46
	256	10	10	9	10	0	1	0	96,66		
	128	10	9	9	9	1	1	1	90		

	64	10	8	8	7	2	2	3	76,66		
	32	10	6	6	6	4	4	4	60		
	16	10	3	2	2	7	8	8	23,33		
	8	10	0	0	0	10	10	10	0		
	4	10	0	0	0	10	10	10	0		
	2	10	1	1	0	9	9	10	6,66		
	1	10	0	0	0	10	10	10	0		
	0,5	10	0	0	0	10	10	10	0		
1c	512	10	7	8	9	3	8	9	80	**66,1**	48,45 -89,95
	256	10	9	7	9	1	4	1	80		
	128	10	8	6	9	2	3	1	80		
	64	10	5	6	7	5	4	3	60		
	32	10	0	1	2	10	9	8	10		
	16	10	1	0	0	9	10	10	3,33		
	8	10	0	0	0	10	10	10	0		
	4	10	0	0	0	10	10	10	0		
	2	10	0	0	0	10	10	10	0		
	1	10	0	0	0	10	10	10	0		
	0,5	10	0	0	0	10	10	10	0		
1d	512	10	10	10	10	0	0	0	100	**20,99**	18,35 - 24,00
	256	10	10	9	10	0	1	0	96,66		
	128	10	10	10	9	0	0	0	96,66		
	64	10	9	8	9	1	2	1	86,66		
	32	10	6	7	6	4	3	4	63,33		
	16	10	5	6	5	5	4	5	36,66		
	8	10	3	2	3	7	8	7	26,66		
	4	10	1	0	0	9	10	10	3,33		
	2	10	0	0	0	10	10	10	0		
	1	10	0	0	0	10	10	10	0		
	0,5	10	0	0	0	10	10	10	0		
T	**/**	**10**	**0**	**0**	**1**	**10**	**10**	**9**	**/**	**3,33**	

CONCLUSION

The antibacterial activity results of the studied synthesized compounds revealed that the sulfonamides **1b-d** showed very good inhibitory characteristics. Their antibiotic properties have promising applications in the control of bacterial infections, especially with the absence of cytotoxic effect.

Among the screened molecules, sulfonamide **1a** was inactive against all the Gram-negative isolates; however, a significant cytotoxic activity was obtained with the same compound allowing us to evaluate its antitumor effect using tumor cell lines.

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