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Synthesis and antibacterial activity of sulfonamides. SAR and DFT studies

Wahida Boufas [a], Nathalie Dupont [b,*], Malika Berredjem [a,*], Kamel Berrezag [a], Imène Becheker [c], Hajira Berredjem [c], Nour-Eddine Aouf [a]

[a] Laboratory of Applied Organic Chemistry, Synthesis of Biomolecules and Molecular Modelling Group, Badji-Mokhtar. Annaba University, Box 12, 23000 Annaba, Algeria
[b] Laboratoire CSPBAT, CNRS (UMR 7244), Université Paris 13, Bobigny, France
[c] Laboratory of Cell Toxicology, General Direction of Scientific Research and Technological Development, Algeria

HIGHLIGHTS

- Best yields for the synthesis of sulfonamides are obtained.
- The activity against clinical strains Gram-positive and Gram-negative was evaluated.
- SAR studies and correlations between DFT computed based chemical descriptors and biological activities are established.

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ABSTRACT

A series of substituted sulfonamide derivatives were synthesized from chlorosulfonyl isocyanate (CSI) in tree steps (carbamoylation, sulfamoylation and deprotection). Antibacterial activity *in vitro* of some newly formed compounds investigated against clinical strains Gram-positive and Gram-negative: *Escherichia coli* and *Staphylococcus aureus* applying the method of dilution and minimal inhibition concentration (MIC) methods. These compounds have significant bacteriostatic activity with totalities of bacterial strains used. DFT calculations with B3LYP/6-31G(d) level have been used to analyze the electronic and geometric characteristics deduced for the stable structure of three compounds presenting conjugation between a nitrogen atom N through its lone pair and an aromatic ring next to it. The principal quantum chemical descriptors have been correlated with the antibacterial activity.

Introduction

Sulfonamides have received considerable attention due to their diverse biological activities as HIV protease [1,2], agonists of the 5-HTID receptor [3,4], carbonic anhydrase inhibitors [5,6], antitumor [7], glycogen phosphorylase inhibitory [8], and cholestrolacyl transferase inhibitory [9].

In recent year, new sulfonamides were described such as doripenem **1**, it is available in brand names doribax is an ultra-broad spectrum injectable antibiotic [10]. Sulfonamide drugs acetazolamide AZA and methazolamide MZA are widely used clinically, mainly as anti-glaucoma agents but also for the therapy of other diseases [11–13]. Compound **2** is an anticonvulsant drug [14]. Sulfonate esters are well-known alkylating agents and cell proliferation inhibitors [15], while sulfonamide derivatives are clinically used as antibacterial and antibiotic medicines [16–19] (see Fig. 1).

On the other hand, sulfonamide inhibits the activity of the enzyme dihydropteroate synthase (DHPS) [20], preventing the synthesis of folic acid (Vitamin B9); intermediate necessary for life of certain bacteria. Apart from the commercialized application as antibacterial/antibiotic agents, various sulfonamides are also known to inhibit several enzymes such as carbonic anhydrase [21], serine protease [22], matrix metalloproteinase [23] and cyclooxygenase [24]. Moreover, the widespread potential value of sulfonamides, have led to the discovery of various other therapeutic applications, in cancer chemotherapy, diuretics [25], hypoglycemia and the anti-impotence agent Viagra [26].

The most practical methods for the synthesis of sulfonamides, involve the sulfonation of alcohols and amines [27,28] in the presence of basic catalysts like pyridine, triethylamine, and aqueous metal hydroxydes.

In this work we have developed the synthesis of new series of modified sulfonamides starting from chlorosulfonyl isocyanate and primary amine. Antibacterial activity of the sulfonamide

* Corresponding authors. Tel.: +213 773875634; fax: +213 38872989 (M. Berredjem).
E-mail addresses: nathalie.dupont@univ-paris13.fr (N. Dupont), malika.berredjem@univ-annaba.org (M. Berredjem).

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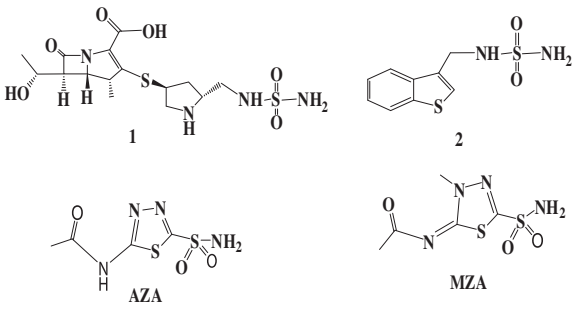

Fig. 1. Example of drugs with sulfonamide functionality.

derivatives **2a–d** was tested on *Escherichia coli* and *Staphylococcus aureus*. Molecular geometries and electronic structures of the three most active compounds have been discussed. Structure–activity relationships (SAR) allow a correct correlation with biological activity with some appropriate quantum descriptors such as E_{HOMO}, E_{LUMO}, energy gap, dipolar moment, global hardness and molecular polarizability [29].

Results and discussion

Chemistry synthesis

In this research the sulfonamides presented here were obtained in three steps from a simple and efficient methodology described below (see Scheme 1):

The carboxylsulfamides (**1a–f**) were prepared by an efficient method [30–33], 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 **(1a–f)** was carried out in distilled water at 100 °C for 30–60 min to give sulfonamides **(2a–f)** with quantitative yields. The structure of all compounds was confirmed by usual spectroscopic methods: ^{1}H NMR, ^{13}C NMR, mass spectrometry and IR.

In vitro antibacterial activity

In this study, we carried out an antibacterial evaluation *in vitro* of a series of four synthetic sulfonamides (**2a**, **2b**, **2c** and **2d**), against Gram-positive and Gram-negative clinical strains isolated from patients presenting different infections: *E. coli*, and *S. aureus* (see Table 1).

These new compounds showed good antibacterial activity towards 6 strains: 4 clinical strains and 2 reference strains. In fact, the diameters of the inhibition zones vary between 13 and 34 mm (Fig. 2).

The results showed that among the tested strains, those presenting sensitivity to the new molecules with an inhibition zones $\geqslant$14 mm are as follows: 6 strains for Mol 2a, 6 strains for Mol 2b, and 4 strains for Mol 2c. Strains of *E. coli* showed resistance towards the Mol 2d.

The most interesting results are those with *S. aureus* witch showed the best antibacterial activity with inhibition zones ranged between 15 and 34 mm. The obtained values for the new compounds are higher than those of Trimethoprim/sulfamethoxazole used as control. This is reflecting a significant antibacterial activity against these multi-resistant strains. The minimum inhibition concentrations (MIC) obtained for the four molecules vary between 2 and 512 μg/ml for most strains (Fig. 3). Best MIC is obtained for the 2a molecule, especially for *Staphylococcus strains* (2 μg/ml for strain St2). For the sulfonamides 2b and 2c, the MIC is ranged between 32 and 256 μg/ml. The molecule 2d has the highest MIC ranging between 256 and 512 μg/ml.

In conclusion, the newly synthesized molecules have a remarkable biological interest. However, 2a molecule showed better activity compared to 2b and 2c molecules, especially for *Staphylococcus* and *E. coli* strains witch MIC vary between 2 and 128 μg/ml. The molecule 2d has shown sensitivity only against *S. aureus*; the inhibition zones are very important but the MIC is very high.

Table 1
Antibacterial activity of the new sulfonamides **2a**, **2b**, **2c**, and **2d**.

Bacterial strains	Mol 2a		Mol 2b		Mol 2c		Mol 2d	
	DZI (mm)	MIC μg/ml	DZI (mm)	MIC μg/ml	DZI (mm)	MIC μg/ml	DZI (mm)	MIC μg/ml
Ec ATCC								
25,922	18	64	22	16	13	2	R	–
Ec 1	20	128	16	128	15	128	R	–
Ec 3	16	64	15	256	15	256	R	–
St ATCC								
25,923	15	4	15	32	16	128	34	256
St 2	16	4	15	64	14	256	34	256
St 3	15	2	14	64	13	128	26	512

MIC: Minimum Inhibitory Concentration.
DZI: Diameter of Zone Inhibition.

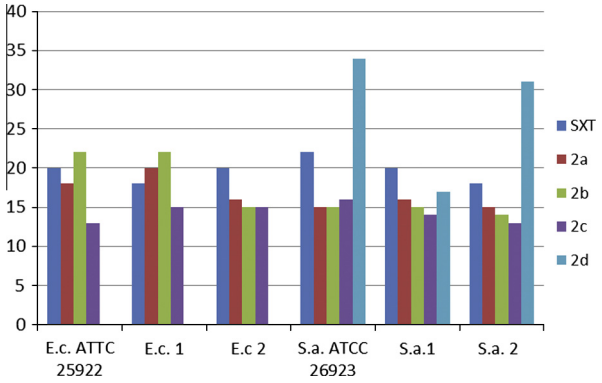

Fig. 2. The inhibition zones of compounds **2a**, **2b**, **2c**, **2d**.

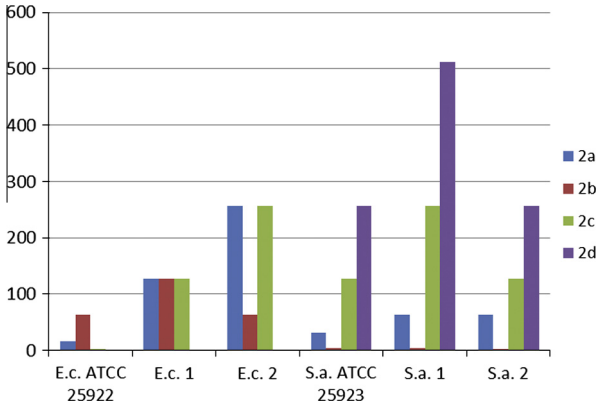

Fig. 3. The minimum inhibition concentration of compounds **2a**, **2b**, **2c**, **2d**.