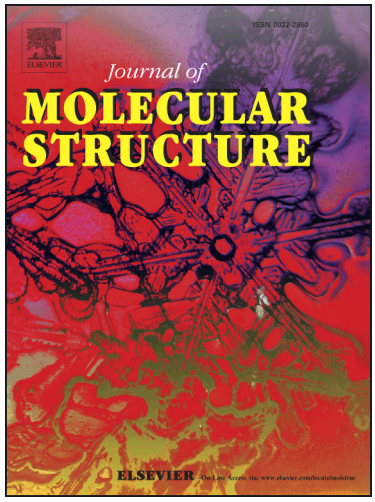

Synthesis and antibacterial activity of sulfonamides. SAR and DFT Studies

Wahida Boufas, Nathalie Dupont, Malika Berredjem, Kamel Berrezag, Imène Becheker, Hajira Berredjem, Nour-Eddine Aouf

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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] and 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.

E-mail: malika.berredjem@univ-annaba.org (M. Berredjem), nathalie.dupont@univ-paris13.fr (N. Dupont)

HIGHLIGHTS

- Best yields for the synthesis of sulfonamides are obtained.
- The activity against clinical strains Gram-positive and Gram-negative was evaluated.
- Computed quantum chemical descriptors based upon DFT calculations have been used to correlate with biological activity in SAR studies

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.

Keywords: sulfonamide, antibacterial activity, molecular modeling, SAR, DFT.

1. 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].

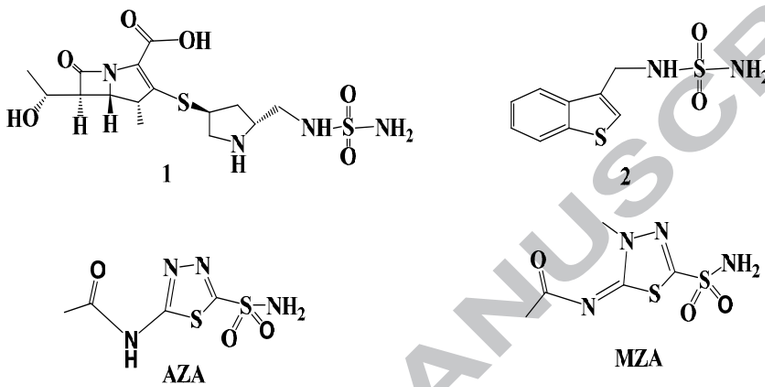


Fig. 1. Example of drugs with sulfonamide functionality

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], hypoglyceamia and the anti-impotence agent Viagra [26].

The most pratical 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.

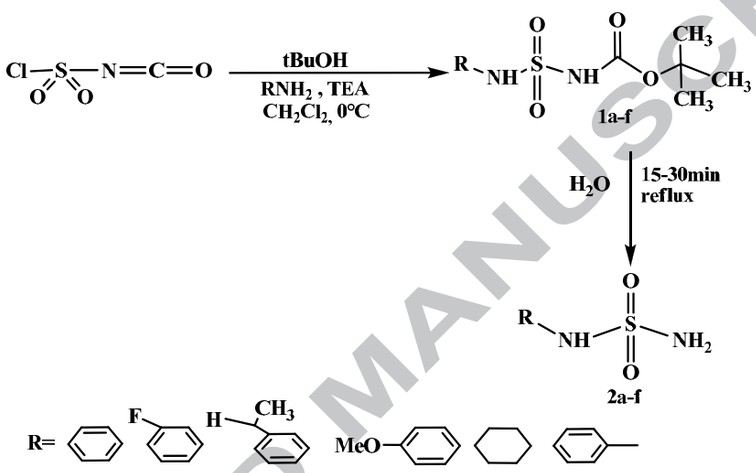
In this work we have developed the synthesis of new series of modified sulfonamides starting from chlorosulfonyl isocyanate and primary amine. Antibacterial activity of the sulfonamide derivatives **2a-d** was tested on *Eschrichia coli and Staphylococcus aureus.* Molecular geometries and electronic 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].

2. Results and Discussion

2-1 *Chemistry Synthesis*

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

The carboxylsulfamides (**1a-f)** were prepared by an efficient method, [30-33] implying the reaction of the tert-butanol and chorosulfonyl 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 sulphate 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, C^{13} NMR, mass spectrometry and IR.



Scheme 1. Synthesis of sulfonamides

2-2 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: *Escherichia coli*, and *Staphylococcus aureus.*

Table 1

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

	Mol 2a		Mol 2b		Mol 2c		Mol 2d	
Bacterial Strains	**DZI (mm)**	**MIC µg/ml**	**DZI (mm)**	**MIC µg/ml**	**DZI (mm)**	**MIC µg/ml**	**DZI (mm)**	**MIC µg/ml**
Ec ATCC	18	64	22	16	13	2	R	-
25922	20	128	16	128	15	128	R	-
Ec 1	16	64	15	256	15	256	R	-
Ec 3	15	4	15	32	16	128	34	256
St ATCC	16	4	15	64	14	256	34	256
25923	15	2	14	64	13	128	26	512
St 2								
St 3								

MIC : Minimum Inhibitory Concentration
DZI : Diameter of Zone Inhibition

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 (Figure 2).

The results showed that among the tested strains, those presenting sensitivity to the new molecules with an inhibition zones ≥ 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 (Figure 3). Best MIC is obtained for the 2a molecule, especially for *Staphylococcus strains* (2µg/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.

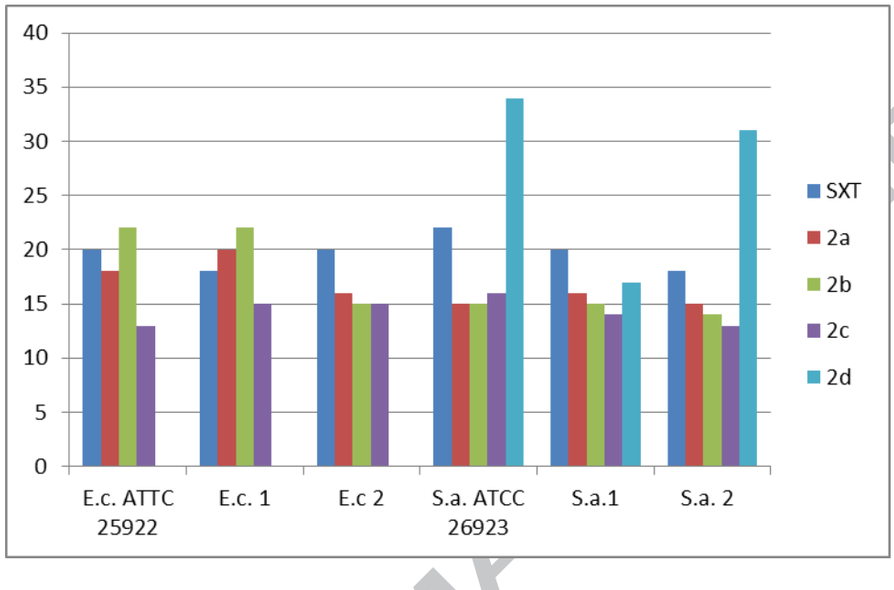


Fig. 2. The inhibition zones of compounds **2a, 2b, 2c, 2d**

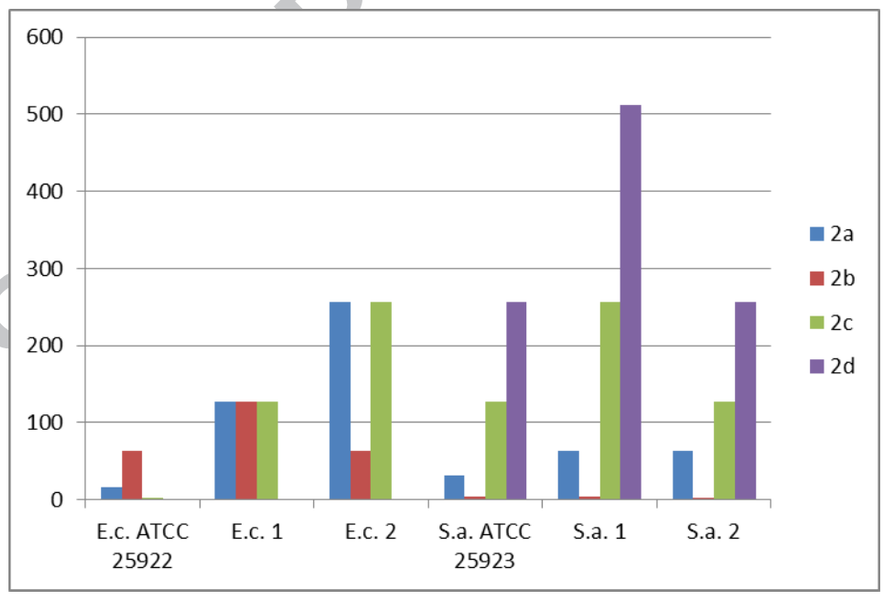


Fig. 3. The minimum inhibition concentration of compounds **2a, 2b, 2c, 2d.**

3-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 Brüker 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 Micro Mass ZQ. All reactions were monitored by TLC on silica Merck h60 F254 (Art. 5554) precoated alumium plates and were developed by spraying with ninhydrin solution.

The inhibition zones of these compounds were determined by the disk diffusion method with a base of Mueller Hinton agar medium inoculated with each bacteria suspension.

The Minimal inhibitory concentrations (MIC) of the compounds were determined by the broth dilution method. The compounds under the test were dissolved in the pure acetone whit geometric dilutions of reason 2 ranging from 0.5 to 512 µg/ml.

3.1. General Procedure for the preparation of sulfonamide

The deprotection reaction of sulfonamide (1a-f) was carried out in distilled water, the reaction mixture was refluxed for 15-30 min, and then it was extracted 3× (30 ml) with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure, to give sulfonamides (2a-f) in good yields

N-(1-phenyl)sulfamide 2a

White solid, yield: 90%. M = 172 g/mol [$C_6H_8N_2O_2S$]. mp: 96-98°C. R_f = 0.55 (CH_2Cl_2/MeOH:9/1). ^{1}H NMR (DMSO, δ ppm): 7.65-7.20 (m, 5H, H-Ar); 4.90 (s, 2H, NH_2).^{13}C NMR (DMSO, δ ppm): 136; 129.58; 125.29; 120.82. IR (KBr, υ cm^{-1}): 3368-3257(NH, NH_2); 1658(C=C); 1364.8 and 1159 (SO_2). MS-ESI+ 30ev m/z: 173 $[M+H]^+$. Anal. Calcd for $C_6H_8N_2O_2S$ (172): C, 41.85; H, 4.68; N, 16.27. Found: C, 41.80; H, 4.61; N, 16.23.

N-(3-flurophenyl)sulfamide 2b

White solid, yield: 78%. M = 190 g /mol [$C_6H_7FN_2O_2S$]. mp: 91-93°C. R_f =0.68 (CH_2Cl_2/MeOH:9/1). ^{1}H NMR (DMSO, δ ppm): 7.75-7.55 (m, 4H, H-Ar); 4.70 (s, 2H, NH_2).^{13}C NMR (DMSO, δ ppm): 164; 139; 129; 119; 111; 105. IR (KBr, υ cm^{-1}): 3370-3262 (NH, NH_2); 1652(C=C); 1361 and 1155 (SO_2). MS-ESI+ 30ev m/z: 191 $[M+H]^+$. Anal. Calcd for $C_6H_7FN_2O_2S$ (190): C, 37.89; H, 3.71; N, 14.73. Found: C, 37.91; H, 3.74; N, 14.78.

N-(1-phenylethyl)sulfamide 2c

White solid, yield: 91%. M = 200 g /mol [$C_8H_{12}N_2O_2S$]. mp:100-102-176 °C. R_f =0.58 (CH_2Cl_2/MeOH:9/1). ^{1}H NMR (DMSO, δ ppm): 7.35 (m, 5H, H-Ar); 5.25 (d, 1H, J= 6.93Hz, NH-CH); 4.55 (m, 1H, CH*);4.45 (S, 2H, NH_2);1.57 (d, 3H, J= 6.93 Hz, CH_3).^{13}C NMR (DMSO, δ ppm): 145; 130; 125.1; 125; 43; 19. IR (KBr, υ cm^{-1}): 3373-3260 (NH, NH_2); 1642 (C=C); 1360 and 1153 (SO_2). MS-ESI+ 30ev m/z: 201 $[M+H]^+$. Anal. Calcd for $C_8H_{12}N_2O_2S$ (200): C, 47.98; H, 6.04; N, 13.99. Found: C, 47.91; H, 6.18; N, 13.96.

N-(4-methoxy-phenyl)sulfamide 2d

White solid, yield: 90%. M = 203 g/mol [$C_7H_{10}N_2O_3S$]. mp: 98-100°C. R_f= 0.62 (CH_2Cl_2/MeOH:9/1). ^{1}H NMR (DMSO, δ ppm): 7.60-7.20 (m, 4H, H-Ar); 4.90 (s, 2H, NH_2), 3.95 (s, 3H, CH_3-O). ^{13}C NMR (DMSO, δ ppm): 136; 129.58; 125.29; 120.82. IR (KBr, υ cm^{-1}): 3368-3257 (NH, NH_2); 1658 (C=C); 1364.8 and 1159 (SO_2). MS-ESI+ 30ev m/z: 204 $[M+H]^+$. Anal. Calcd for $C_7H_{10}N_2O_3S$ (203): C, 44.43; H, 5.59; N, 12.95. Found: C, 44.51; H, 5.61; N, 12.96.

N-(1-cyclohexyl)sulfamide 2e

White solid, yield: 87%. M = 178 g /mol [$C_6H_{14}N_2O_2S$]. mp: 85-87 °C. R_f =0.6 (CH_2Cl_2/MeOH:9/1). ^{1}H NMR (DMSO, δ ppm): 4.90 (d, 1H, J = 6.2, NH cyc); 3.60 (s, 2H, NH_2); 3,25 (m, 1H, CH*NH), 1.85 (m, 2H, CH_2 cyc), 1,55 (m ,2H, CH_2-cyc), 1,35 (m , 2H, CH_2-cyc); 1,25 (m, 4H, $2CH_2$-cyc). ^{13}C NMR (DMSO, δ ppm): 42.9; 33.5; 26.1; 25.9; 20. IR (KBr, υ cm^{-1}): 3374-3269 (NH, NH_2); 1368 and 1150 (SO_2). MS-ESI+ 30ev m/z: 179 $[M+H]^+$. Anal. Calcd for $C_6H_{14}N_2O_2S$ (178): C, 40.43; H, 7.92; N, 15.72. Found: C, 40.40; H, 7.90; N, 15.75.

N-(benzyl)sulfamide 2f

White solid, yield: 80%. M = 186 g /mol [$C_7H_{10}N_2O_2S$]. mp: 97-99°C. R_f = 0.48 (CH_2Cl_2/MeOH:9/1). ^{1}H NMR (DMSO, δ ppm): 7.70-7.90 (m, 5H, H-Ar); 4.90 (s, 2H, NH_2); 3.65 (m, 2H, CH_2-Ar); ^{13}C NMR (DMSO, δ ppm): 136; 129.58; 125.29; 120.82; 43.6. IR (KBr, γ cm-1): 3368-3257(NH, NH_2); 1658(C=C); 1364.8 and 1159 (SO_2). MS-ESI+ 30ev m/z: 186 $[M+H]^+$. Anal. Calcd for $C_7H_{10}N_2O_2S$ (186): C, 45.15; H, 5.41; N, 15.04;. Found: C, 45.19; H, 5.45; N, 15.10.

4-Structure-activity relationship (SAR) and DFT based chemical descriptors.

The ultimate goal of structure-activity relationship (SAR) studies is to correlate the biological activity of a series of compounds with some appropriate descriptors in order to help the design of best active new compounds. The mechanism of antimicrobial action of sulfonamides is well described at the enzyme level. Their antibacterial properties are related to the inhibition of the enzyme dihydropteroate synthase (DHPS) [34]. In bacteria, sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase, DHPS, which catalyses the conversion of PABA (para-aminobenzoic acid) to dihydropteroate, a key step in folate synthesis. Folate is necessary for the cell to synthesize nucleic acids (DNA and RNA), and in its absence, cells will be unable to divide. Hence, sulfonamides exhibit a bacteriostatic rather than bactericidal effect. Design of our compounds is based on the key functions described on Figure 4. In Such compounds with antibacterial activity, a sulfonamide group may provide a hydrogen bonding interaction with a specific amino acid of the enzyme backbone and an aryl group that may have effective Van der Waals interactions with enzyme subsites.

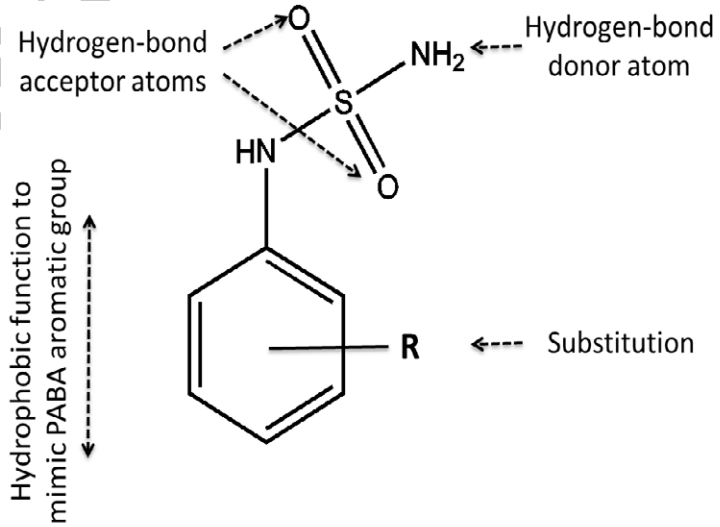


Fig. 4. Key functions in the antibacterial design of sulfonamides derivatives.

Unconstrained geometry optimizations of titled compounds 2a ,2b and 2d were carried out at gradient corrected DFT using Becke's three parameters hybrid method and the Lee -Yang - Parr correlation functional (B3LYP) [35] combined with 6-31G(d) basis set [36] using Gaussian 09 [37] in both gas and solvent (DMSO) media. The studied compounds were characterized as minima (no imaginary frequency, stationary point found) in their potential energy surface. In 2c, the nitrogen atom N is no more conjugated with the aromatic ring through its lone pair and can't be used for a SAR study and comparison involving compounds 2a, 2b and 2d. Concerning antibacterial activity of compounds 2a, 2b and 2d, 2a is studied as the most active compounds then 2b and finally 2d.

The computed quantum chemical descriptors based upon DFT calculations in both gas and solvent (DMSO) media are presented in Table 2. Figure 5 shows the optimized structures obtained by B3LYP/6-31G(d) level in solvent phase (DMSO).

Table 2
Quantum chemical descriptors based upon DFT calculations used for SAR hypothesis for compounds 2a, 2b and 2d.

Quantum descriptors	**Gas phase**			**Solvent phase (DMSO)**		
	2a	2b	2d	2a	2b	2d
E_{LUMO} (eV)	-0.22	-0.45	-0.19	-0.35	-0.53	-0.34
E_{HOMO} (eV)	-6.32	-6.45	-5.84	-6.49	-6.54	-6.04
ΔE_{gap} (eV)	6.10	6.00	5.65	6.14	6.01	5.70
Average linear polarizability α_{Tot} (Bohr^3)	94	95	112	120	120	142
Total dipole moment μ (D)	2.98	4.02	3.18	4.07	5.34	4.17

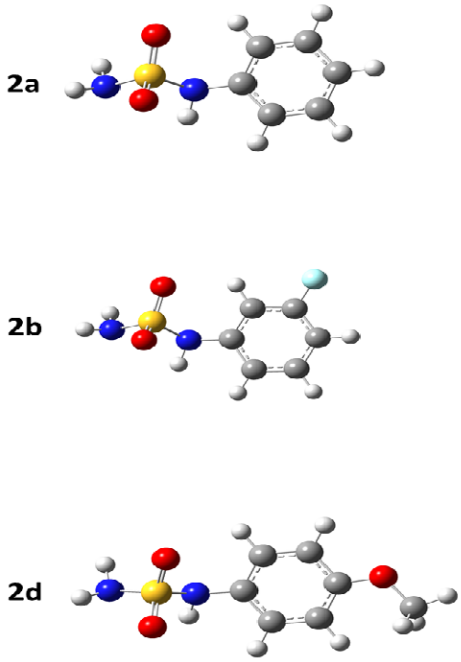


Fig. 5. Optimized structures of 2a (top), 2b (middle) and 2d (bottom) obtained at B3LYP/6-31G(d) level in DMSO.

Carbon atoms are represented with grey spheres, Oxygen with red, Nitrogen with blue, sulfur with yellow, fluoride with cyan and hydrogen with white spheres.

Frontier molecular orbitals were performed at the same level of theory. The frontier orbitals, HOMO and LUMO, determine the way a molecule interacts with other species. The energies of frontier molecular orbitals are important properties in several chemical and pharmacological processes [38]. The value of E_{HOMO} is often associated with the electron donating ability of inhibitor molecules, higher values of E_{HOMO} is an indication of the greater ease of donating electrons to the unoccupied orbital of the receptor. The value of E_{LUMO} is related to the ability of the molecule to accept electrons, the smaller the E_{LUMO} is, the smaller the resistance to accept electron will be. According to Koopman's theorem, the ionization energy (I) and electron affinity (A) can be expressed through HOMO and LUMO orbital energies as $I = -E_{HOMO}$ and $A = - E_{LUMO}$ [39]. Substituents have a stronger effect on the energy of the HOMO than of the LUMO. In 2b, the fluorine atom has a withdrawing effect that lowers the HOMO and LUMO energies compared to 2a. In 2d, there is a significant effect of the donor methoxy group that increases the energy of the HOMO.

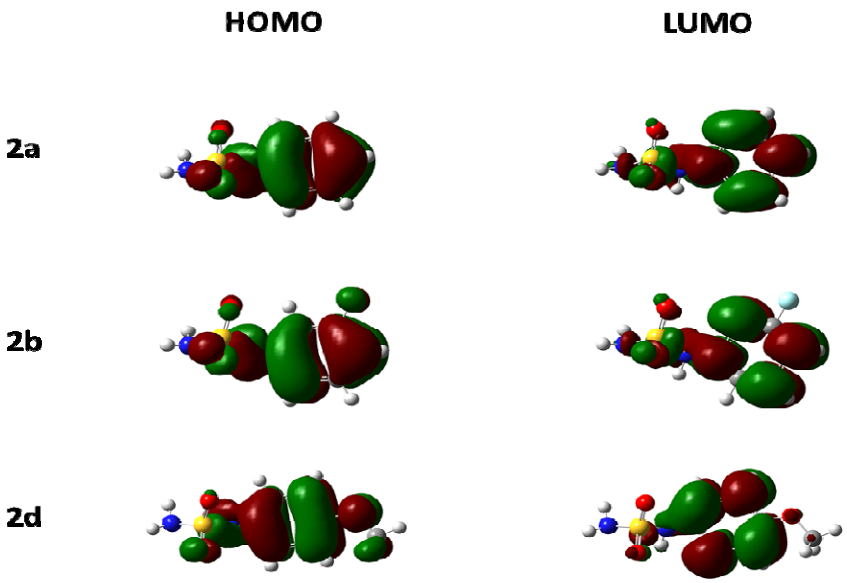


Fig. 6. Frontier orbitals for 2a, 2b and 2d obtained at the B3LYP / 6-31G(d) level using a contour threshold of 0.02 a.u.

Figure 6 shows HOMO and LUMO frontier orbitals obtained at the same level using a contour threshold of 0.02 a.u. for the studied compounds. It is important to examine the HOMO and LUMO for these compounds because the relative ordering of occupied and virtual orbital provides a reasonable qualitative indication of electronic properties. In general, the HOMO possesses an antibonding character between the consecutive subunits, whereas the LUMO generally shows a bonding character between the subunits. No direct correlation between HOMO or LUMO energies and antibacterial activities is highlighted.

The gap in energy between the HOMO and LUMO is an important stability index [40]. A large gap implies high stability and small gap implies low stability. Generally, the high stability indicates low chemical reactivity and small gap indicates high chemical reactivity. Another very useful theory of electronic structure and reactivity of molecules involving the single pair of frontier orbitals is the Hard–Soft Acid Base (HSAB) principle of Pearson [41]. Softness (S) is a property of molecule that measures the extent of chemical reactivity. It is defined as the reciprocal of hardness (η) with $\eta = (I - A)/2$ that is directly related to ΔE_{gap} [42]. The soft molecules undergo changes in electron density more easily than the hard molecules. Polarizability (α) measures the ability of electrons in a molecule to move easily as a result of stimulus. The softer a molecule is, the higher is its average polarizability. Herein is verified a direct correlation between hardness and antibacterial activity. With the biggest gap value of 6.14 eV in DMSO, 2a is the most active, the hardest compound and is associated with the lowest polarizability value. It could be related to a predominance of electrostatic interaction in the binding enzyme site.

The dipole moment (μ in Debye) is frequently another important electronic parameter that results from non-uniform distribution of charges on the various atoms in a given molecule. It is frequently used to study the intermolecular interactions involving the non-bonded type dipole – dipole interactions, because higher the dipole moment is, stronger are the intermolecular interactions. Herein, no direct correlation with activity can be highlighted.

Finally, the molecular electrostatic potential surface MESP, that is a plot of electrostatic potential mapped on the iso-electron density surface, simultaneously displays shape and electrostatic potential values. It has been plotted for compounds 2a, 2b and 2d on Figure 7. Molecular electrostatic potential mapping is very useful in the investigation of the physicochemical properties of the studied compounds. Different values of the electrostatic potential at the surface are represented by different colours: red represents regions of most electro negative potential, blue represents regions of most positive electrostatic potential and green represents

regions of zero potential. Herein, the three MESPs are very similar and revealed that the high electronic density suitable for electrophilic attack is located on sulfonyl oxygen atoms in the red region. Alternatively, analysis of the mulliken charge in DMSO revealed that sulfonyl oxygen atoms bear an average charge of -0.538 in 2a, -0.535 in 2b and -0.544 in 2d whereas nitrogen next to the aromatic cycle bear a charge of -0.756 in 2a, -0.760 in 2b and -0.756 in 2d and the other nitrogen bear a charge of -0.820 in the three compounds. On the other hand, MESPs reveals two majors nucleophilic active centers at the proximity of hydrogens atoms linked to nitrogen atoms, with an average Mulliken charge of 0.385 and a third nucleophilic center in 2d due to the presence of methoxy group.

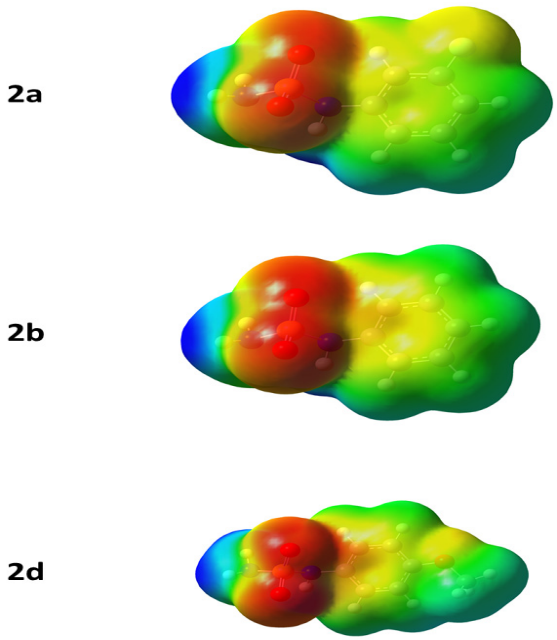


Figure. 7. Molecular electrostatic potential map for 2a (top), 2b (middle) and 2d (bottom) on total density. (Isovalue = 0,0004 a.u.). potential ranges from almost -50 kcal.mol^{-1} (-0.08 a.u - red color) to +50 kcal.mol^{-1} (+0.08 a.u - blue color).

The theoretical study implies that gap, polarizability and hardness tend to be the best chemical descriptors to identify compounds presenting an interesting antibacterial activity. The reaction of inhibition in question seems to be mainly directed by hard-hard interactions, for example the transfer of a proton to a hard base. In that case, the reactions are mainly controlled by electrostatic relationships as modeled by Mulliken charges that can be also considered as important descriptors.

5-Conclusions

The *N*-aryl sulfonamides derivatives produced compounds with potential with further development as antibacterial agents based on these preliminary screening results, compounds **(2a-d)** showed significant activity against *Eschrichia coli and Staphylococcus aureus*. Compounds under study showed a mean biological activity due the presence of sulfonamide moiety. Meanwhile, compound **2d** proved to have the weakest activity with height MIC and especially for only one bacteria *Staphylococcus aureus*. The theoretical study on 2a, 2b and 2d compounds presenting a conjugation of the nitrogen atom with the aromatic ring through its lone pair allowed us to bring a preliminary SAR study. About antibacterial activity, on the basis of an interaction with the binding site mainly controlled by electrostatic interactions, qualified as hard-hard interactions, the most important descriptors tend to be gap, polarizability and Mulliken charges on

nitrogen and hydrogen atoms. Studies are underway in our laboratory to investigate more derivatives presenting an optimized structure with an optimized antibacterial activity.

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HIGHLIGHTS

- Best yields for the synthesis of sulfonamides are obtained.
- The activity against clinical strains Gram-positive and Gram-negative was evaluated.
- Computed quantum chemical descriptors based upon DFT calculations have been used to correlate with biological activity in SAR studies