MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

The comparison of semiempirical and ab initio molecular modeling methods in activity and property evaluation of selected antimicrobial sulfonamides

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Abstract

A group of sulfonamides exhibiting antimicrobial activity was analyzed with the application of quantitative structure–activity/property relationships method. The purpose of this study was to show the common and differentiating characteristics of the analyzed chemical structures alike physicochemically as well as pharmacologically based on the quantum-chemical calculations both in vacuo and in the aquatic environment together with their microbiological activity and chromatographic retention data. The semiempirical and ab initio level of in silico molecular modeling was performed for calculations of statistically significant molecular descriptors to compare obtained results. The relationship between the structure and biological activity and physicochemical parameters data was able to class and describe analyzed molecules and the applied chemometric approaches (principal component analysis, factor analysis, and multiple regression analysis) revealed the influential features of the tested structures responsible for the antimicrobial activity.

Keywords Sulfonamides · Molecular modeling · Structural analysis · Principal component analysis · Factor analysis · Multiple regression analysis

Introduction

Antibacterial sulfonamides are one of the oldest groups of chemotherapeutics and therefore the structure–property relationship, and especially the structure–biological activity of this group of compounds was the subject of a number of works. One of the first of these was the finding of the relationships between acid and alkaline dissociation constants and microbiological activity (Bell and Roblin 1942). In addition, one should mention the study of the relationship between the acid dissociation constant and the chemical shift of nuclear magnetic resonance spectra and microbiological activity (Seydel 1971; De Benedetti and Rastelli 1978), the relationship between microbiological activity and data on high-performance liquid chromatography retention (Rastelli et al. 1975; Henry et al. 1976; Brent et al. 1983), and the relationship between microbiological activity and physical parameters such as molar refraction or the sum of the electronegativity values of the atoms that make up the substituent in the sulfonamide group (Kaliszan et al. 1979). Previously, the chemometric analysis was presented covering the dependence of retention data from high-performance liquid chromatography and nonempirical parameters calculated by quantum-chemical methods and other structural parameters and data obtained by ultraviolet spectroscopy, and to a limited extent with the microbiological activity of sulfonamides (Bober et al. 1998). Since the significance of the parameters available from quantum-chemical calculations in the chromatographic structure-retention dependence (QSRR) as well as the structure–biological activity was discussed by Kaliszan

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(1987, 1997, 2007), it would be interesting to carry out such an analysis for data from quantum-chemical calculations using the ab initio method and data available from the literature on both microbial activity in vitro and other parameters conditioning the biological activity of sulfonamides for a slightly broader database, as well as previously determined chromatographic retention parameters and other physicochemical literature data.

In the literature, we can also find other studies with the use of structure–activity together with molecular docking with complexes and toxicity analysis of different antimicrobial sulfonamides (Agrawal et al. 2001; Krátký et al. 2012; Boufas et al. 2014; Singh 2015; Chen et al. 2017; Mondal et al. 2017; Swain et al. 2017; Mizdal et al. 2018; Naaz et al. 2018).

On the other hand, the significance of the parameters available from quantum-chemical calculations in relation to a structure–biological activity for different groups of compounds was as well already confirmed in the previous series of publications (Belka et al. 2012, 2013; Bober et al. 2012a, b; Stasiak et al. 2013; Kawczak et al. 2014, 2015, 2018a, b, c, 2019; Ciura et al. 2017). In view of the above, it was decided to check how the physicochemical descriptors obtained as a result of quantum-chemical methods are influencing the classification of sulfonamides, while all the performed calculations were possible on standard-class principal components. In addition, it would be advisable to determine quantitative relationships between structural parameters derived from quantum-chemical calculations and biological activity, all using standard statistical analysis methods. The subject of this work was to perform analysis for ab initio together with semiempirical data using the RM1 method of both isolated (in vacuo) molecules as well as hydration of molecules and hydrogen bonds for a number of antibacterial sulfonamides and to obtain chemometrically confirmed relationships between physicochemical parameters and biological parameters of antibacterial sulfonamides and nonempirical parameters characterizing their chemical structure.

Materials and methods

Molecules and analytes

The following compounds were selected for the study from the group of antibacterial sulfonamides: 2-sulfapyridine, 3-sulfapyridine, 4-methylsulfathiazole, sulfacarbamide, sulfacetamide, sulfachloropyridazine, sulfadiazine, sulfadimethoxine, sulfaetidol, sulfafurazole, sulfaguanidine, sulfalene, sulfamerazine, sulfamethazine, sulfamethoxydiazine, sulfamethoxypyridazine, sulfamethizole, sulfamethoxazole, sulfamonomethoxine, sulfamoxole, sulfanilamide, sulfaquinoxaline, sulfasomidine, and

sulfathiazole. All structural formulas of analyzed molecules are presented in Fig. 1.

Biological activity and chromatographic retention data

The work uses literature data on microbial activity expressed as $\log 1/MIC$, where MIC means the lowest concentration inhibiting the growth of *Escherichia coli* in vitro in $\mu mol\, dm^{-3}$ (microbial inhibiting concentration) from the work of Krüger-Thiemer and Bünger (1965). In the presented work in the case of sulfonamides, the literature data relevant to the bioavailability and pharmacokinetics were taken from Rieder's work (Von Rieder 1963). These are the binding of sulfonamide to plasma proteins expressed as the logarithm of the inverse (i.e., negative) constant α and logarithm of the constant β in the Langmuir adsorption equation (LG1_ALFA and LG_BETA, respectively) expressed as logarithms in accordance with the concept presented in Brent's paper (Brent et al. 1983). Rieder's constant α is the concentration of sulfonamide in the protein lacking proteins in $\mu mol\, l^{-1}$ at half-saturation with protein adsorption (therefore the reciprocal of the constant is directly proportional to plasma protein binding (PB)) and the constant β is determined as the maximum specific adsorption of sulfonamide on plasma proteins at $\mu mol\, g^{-1}$. The percentage of PB comes from the study of Othmer (2007).

The chromatographic data for some sulfonamides come from works of Koba et al. (2010) and Bober et al. (2011) for XTerra RP-18, XTerra RP-8, IAM PC C10/C3, AGP, Hypersil HSA, Nucleosil 100-5 OH, Discovery HS PEG, IC Pak Anion HR, IC Pak Cation M/D, Spheri Anion AX and Purospher STAR RP-18, Aluspher RP select B, Chromolith RP-18, and Supelcosil Plus ABZ.

Molecular descriptors

Nonempirical structural indicators (quantum-chemical indicators) were calculated during the study. The structure of compounds was studied by molecular modeling using the Gaussian 03W (Gaussian Inc., Wallingford, CT, USA). The geometry of the molecules was optimized using restricted Hartree-Fock 6–-1G (d, p) (6-31G**) (Official Gaussian Website 2019 http://www.gaussian.com/). For compounds for which biological activity data were available, the optimal solutions would be optimization of the structures in aqueous medium, using the method of polarizable continuum model (Tomasi and Persico 1994; Tomasi et al. 2005; Caricato and Scalmani 2011); however, the size of most of the considered molecules on standard-class PC prevented this intention, and therefore we decided to use only ab initio results for the molecules in vacuo. On the other hand, semiempirical

Fig. 1 Structural formulas of compounds studied
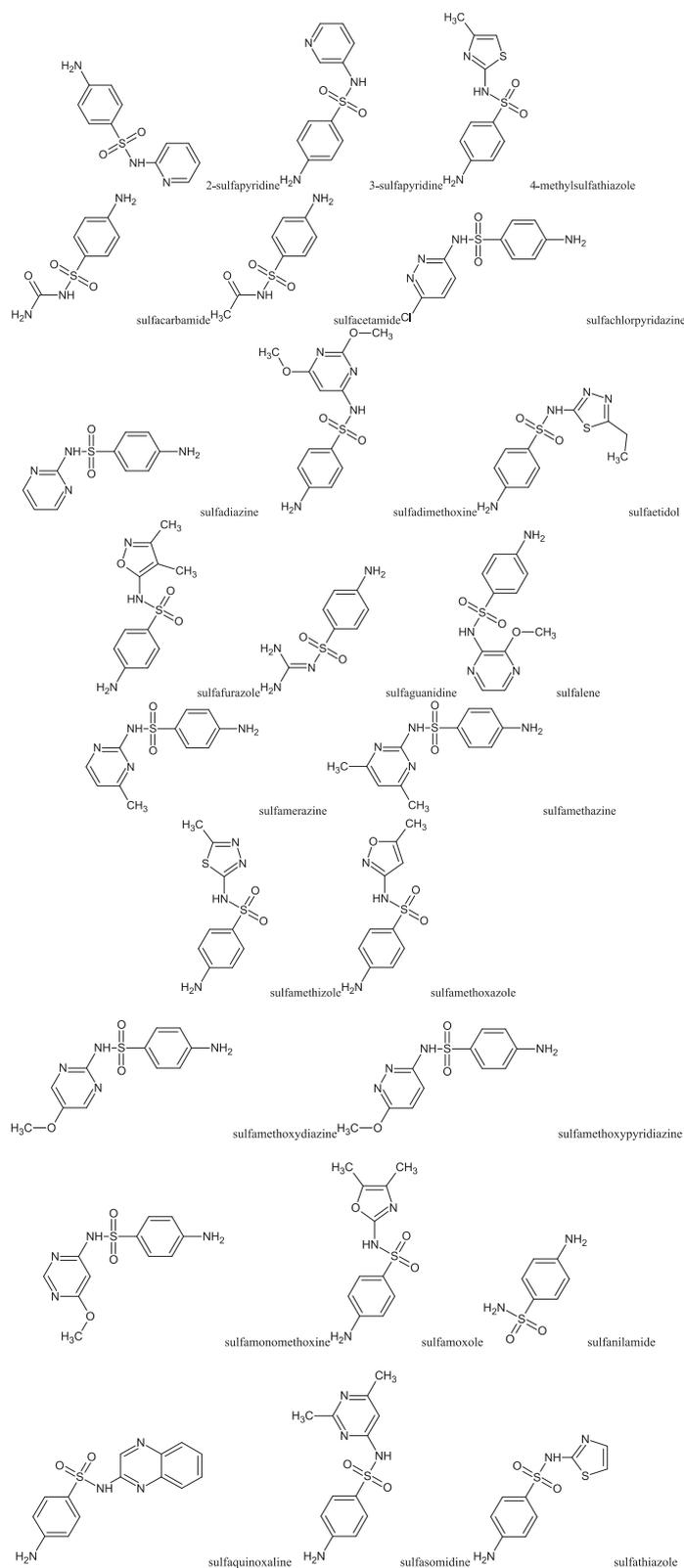
methods for the whole group of analyzed compounds in vacuo and in the aquatic environment were performed. The structures of the tested compounds were studied by molecular modeling using HyperChem v. 8.0 (Hypercube Inc., Gainesville, FL, USA) software. The geometry of the molecule was initially optimized by molecular mechanics MM+ and

then using the semiempirical method RM1 (HyperChem® Computational Chemistry 1996). After completing the optimization, a single-point calculation was performed. The molecule was placed in a periodic box, in which dimensions were selected in such a way that the program has been placed within around 40 water molecules, and the optimization of the geometry was repeated in an environment of water molecules by RM1. Among the quantum-chemical indices were considered: total energy (TE), binding energy (BE), electron energy (EE), heat of formation (HF), energy of the highest-occupied molecular orbital, energy of the lowest vacant molecular orbital (ELUMO), and the difference of HOMO and LUMO energy defined as the energy gap (EG). Moreover, the following values were used: the spatial extent of the electron (ESE), the largest positive charge on the electron atoms (Q + MAX/MAX_POS), the largest negative charge on the electron atoms (Q-MIN/ MAX_NEG), the difference between the largest positive and negative charge (ΔQ/DELTA_Q), total dipole moment (TDM), the isotropic polarizability (IPOL) the mean polarizability (MPOL), and energy values for the most long-term transition of electron (EL) for which a power oscillator >0. The values of TE were expressed in atomic energy units (a.u.) = Hartree (1 Hartree = 2625.552 and 627.5095 kcal × mol^{-1} or 27.2116 eV), energy HOMO, LUMO, and EG expressed in eV (converted the above values into eV), and electron spatial extent of eBohr^{-3}. The values of electron density and electron charges on the atoms were expressed in units of elementary charge (e^-), dipole moment expressed in Debye (D), and the average polarizability in Bohr^3 (Bohr = 0.5292 × 10^{-10} m = 0.5292 Å). For the structures optimized in aqueous medium, the following additional parameters were used: the surface of the molecule accessible to the solvent (SA), expressed in Å^2, the volume of the molecule (V) in Å^3, and the hydration energy (HE) in kcal mol^{-1} for both types of structures optimized by RM1 in vacuo and in the surrounding water molecules.

Furthermore, for the whole group of molecules, Dragon 7.0 (Kode Chemoinformatics, Pisa, Italy) software was used to calculate a huge set (>5200) of extra descriptors (Todeschini and Consonni 2010; Dragon 7 molecular descriptors 2019 https://chm.kode-solutions.net/products_dragon.php).

Statistical analysis

The data that examined the biological activity of compounds were related to their structural indicators using multiparametric regression analysis/multiple regression analysis with a stepwise progressive method together with principal component analysis (PCA) and factor analysis (FA) implemented in Statistica 13 (StatSoft, Tulsa, OK, USA) on a personal computer. In PCA, a matrix of

Table 1 Biological activity values of some antimicrobial sulfonamides

No.	Compound	Log 1/MIC	α	β	PB
1	2-Sulfapyridine	−0.79	–	–	70
2	3-Sulfapyridine	−0.30	–	–	–
3	4-Methylsulfathiazole	−0.30	–	–	–
4	Sulfacarbamide	−1.51	–	–	–
5	Sulfacetamide	−0.52	1432	13.3	9.5
6	Sulfachloropyridazine	–	100	32.4	–
7	Sulfadiazine	−0.08	970	27.8	37.8
8	Sulfadimethoxine	0.06	6.5	26.2	92.3
9	Sulfaetidole	−0.34	15	31.1	–
10	Sulfafurazole	−0.45	54	25.2	76.5
11	Sulfaguanidine	−1.81	–	–	–
12	Sulfalene	−0.20	–	–	–
13	Sulfamerazine	0.06	169	21.7	–
14	Sulfamethazine	0.11	192	28.0	66
15	Sulfamethizole	−0.50	–	–	22
16	Sulfamethoxazole	0.06	320	33.9	60
17	Sulfamethoxydiazine	–	80	26.1	–
18	Sulfamethoxypyridazine	0.00	56	25.5	77
19	Sulfamonomethoxine	–	60	20.2	–
20	Sulfamoxole	–	146	33	76.5
21	Sulfanilamide	−2.11	965	6.4	9
22	Sulfasomidine	–	60	20.7	67
23	Sulfathiazole	−0.18	280	32.8	68

MIC lowest concentration inhibiting the growth of *Escherichia coli*, α concentration of sulfonamide in the protein lacking proteins at half-saturation with protein adsorption, β maximum specific adsorption of sulfonamide on plasma protein constant, *PB* value of protein binding

correlations has been diagonalized, and in FA, Varimax rotation has been performed.

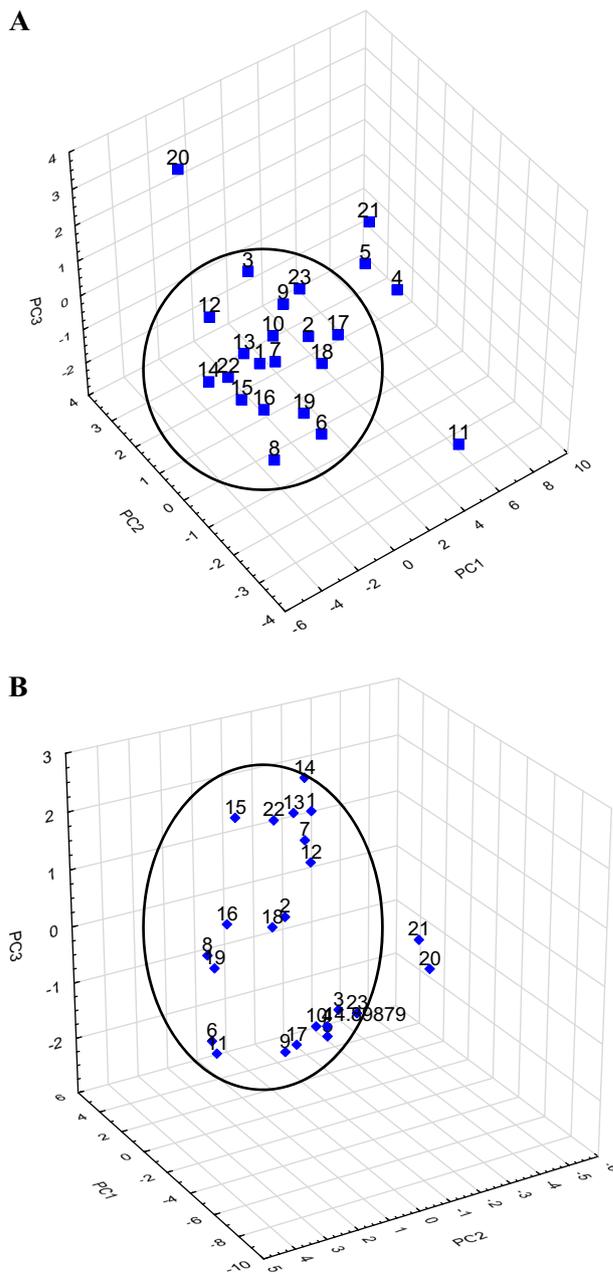## Results and discussion

The numerical values of all 10 structural parameters derived from quantum-chemical calculations in vacuo from Gaussian software for the selected 24 antimicrobial sulfonamides are shown in Table 1S, the values of 16 parameters for the optimized structures in vacuo from HyperChem software are presented in Table 2S, and the structures in the aquatic environment in Table 3S are analyzed during the study. Table 1 presents the biological activity values for the sulfonamides and Table 2 presents the retention parameters obtained for the selected sulfonamides.

First of all, the analysis of PCA was performed for the geometry-optimized structures both for the isolated molecules or in a vacuum and in the aquatic environment to compare structural resemblance between the analyzed molecules.

Table 2 Chromatographic retention parameters of selected antimicrobial sulfonamides

Compound	Log k XT RP18 2	Log k XT RP18 7	Log k XT RP18 11	Log k XT RP8 7	Log k XT RP8 11	Log k IAM 2	Log k IAM 7	Log k DPEG 2	Log k DPEG 7	Log k AGP	Log k HSA	lg kw PS2	lg kw PS7	lg kw AI 2	lg kw AI 7	lg kw AI 11	lg kw Ch 2	lg kw Ch 7	lg kw SABZ +2	lg kw SABZ +7	lg k NOH 2	lg k NOH 7	lg k ICAn 2	lg k ICAn 7	lg k ICAn 11	lg k AX 2	lg k AX 7	lg k ICCat 2	lg k ICCat 7
Sulfacarbamide	0.6889	0.0222	−0.0807	0.7449	−0.1403	0.5397	−0.1246	0.5103	−0.2545	−0.4034	−0.0607	0.244	−0.850	0.101	−0.544	−0.069	0.747	0.108	1.019	0.227	0.287	0.251	0.743	0.756	0.331	0.381	0.761	0.539	−0.028
Sulfacetamide	0.8560	0.1240	−0.0280	0.8974	−0.0655	0.5913	−0.1223	0.4893	−0.2507	−0.5072	0.0813	0.498	−0.766	0.123	−0.577	−0.074	0.973	0.167	1.208	0.465	0.297	0.255	0.688	0.770	0.348	0.177	0.702	0.538	−0.04
Sulfachloropyridazine	1.6564	1.1477	0.6500	1.5876	0.5283	1.2808	0.3890	0.9248	0.1854	−0.1574	0.7124	2.333	1.943	0.605	−0.399	−0.748	2.001	1.594	1.899	1.745	0.433	0.388	1.265	1.595	1.040	0.403	1.433	0.921	−0.058
Sulfadiazine	0.9310	0.5843	0.0482	0.9292	0.0451	0.6501	0.2397	0.4666	0.0768	−0.2503	0.2565	0.646	0.015	0.182	−0.197	−0.066	1.281	0.920	1.327	1.045	0.353	0.367	0.737	0.916	0.494	0.247	0.864	0.745	0.105
Sulfadimethoxine	2.4874	1.7312	0.9604	1.6643	0.8406	1.9094	1.0361	1.4570	0.6423	−0.0788	1.8547	2.507	1.408	1.317	0.524	0.005	2.875	2.001	2.763	1.714	0.559	0.447	1.487	1.542	1.007	0.476	1.45	1.148	0.017
Sulfaguanidine	0.3090	0.4005	0.3941	0.3462	0.4529	0.2270	0.3374	0.1488	0.2867	−0.1029	0.1620	−0.654	−0.517	−0.072	−0.082	0.152	0.410	0.493	0.564	0.702	0.228	0.307	0.439	0.550	0.542	0.240	0.432	0.636	0.413
Sulfamerazine	1.0870	1.0402	0.2457	1.0170	0.1514	0.6969	0.5550	0.3764	0.2770	−0.1135	0.3371	2.025	1.955	0.124	−0.111	−0.779	1.625	1.558	1.543	1.537	0.347	0.389	0.672	0.922	0.559	0.209	0.839	0.823	0.21
Sulfamethazine	1.2676	1.4636	0.6829	1.1225	0.4890	0.7535	0.8444	0.2784	0.4020	0.0170	0.3329	2.103	2.223	0.113	0.093	−0.771	1.895	0.92	1.783	2.003	0.343	0.419	0.554	0.837	0.686	0.150	0.695	0.894	0.344
Sulfamethoxazole	1.6741	0.8515	0.2783	0.6172	0.1735	1.3544	0.3485	1.1361	0.1826	−0.2457	0.3476	2.366	1.649	0.615	−0.382	−0.767	2.148	1.341	2.041	1.407	0.445	0.328	1.334	1.323	0.791	0.413	1.169	0.830	0.039
Sulfamoxole	1.3932	1.4621	0.5457	0.5457	0.4028	0.9223	0.9117	0.3812	0.4186	0.0056	0.4485	2.176	2.207	0.192	0.097	−0.777	1.993	2.111	1.909	2.006	0.377	0.542	0.664	0.990	0.839	0.180	0.826	0.795	0.283
Sulfanilamide	0.3578	0.4411	0.0340	0.3984	0.0030	0.2554	0.3215	0.3025	0.3972	−0.1481	1.1116	−0.292	−0.141	−0.065	−0.072	−0.025	0.457	0.540	0.689	0.781	0.230	0.276	0.630	0.702	0.375	0.135	0.366	0.513	0.368
Sulfaquinoxaline	2.6453	1.9360	1.4187	1.7261	1.3247	2.2575	1.2267	1.7210	0.8681	0.2410	1.8970	2.29	1.68	1.632	0.586	0.18	2.985	2.405	2.997	2.046	0.704	0.630	1.763	2.065	1.499	0.728	1.953	1.390	−0.006
Sulfathiazole	1.1323	1.1589	0.6068	1.1197	0.5618	0.9445	0.9203	0.7106	0.7044	0.1126	0.5518	0.853	0.520	0.321	0.326	0.050	1.524	1.546	1.581	1.678	0.411	0.495	1.006	1.580	1.322	0.481	1.355	0.817	0.345

Fig. 2 Three-dimensional scatter plots of the scores of the first three factors obtained by principal component analysis (PCA) of structural parameters derived from the quantum-chemical calculations in vacuo from the HyperChem software **a** and hydrated from the HyperChem software **b** for 23 antimicrobial sulfonamides (**a** PC1—49.66%, PC2—16.46%, and PC3—13.84%; **b** PC1—45.15%, PC2—17.40%, and PC3—14.90%)

In the case of the selected group of 24 sulfonamides, PCA in vacuo results from Gaussian are as follows: PC1 is around 32.98, PC2 30.72, and PC3 14.33% (Fig. 2). PC1 1 is mainly influenced by an EG, the highest negative charge of the atom of the molecule, TE, and the ELUMOs. PC2 is most influenced again by electron charges on atoms: the highest negative charge of the atom of the molecule, the

ESE, and the IPOL. Analyzing the results of the hydrated form of sulfonamides from HyperChem, we get the following results: PC1 is around 45.15, PC2 17.40, and PC3 14.90%. PC1 1 is mainly influenced by TE, BE, and electron energy, and also EG, the difference between the largest positive and negative loads, the ELUMO, and HE. On the other side, PC2 is most influenced by energy values for the most long-term transition of the electron, the EG and TDM, but also electron energy and BE to a lesser extent. On the other hand, PCA in vacuo results from HyperChem are as follows: PC1 is around 49.66, PC2 16.46, and PC3 13.84%. PC1 1 is mainly influenced by EG, electron energy, TE, and BE,, and also the energy of the lowest vacant molecular orbitals, the difference between the largest positive and negative loads, the highest positive charge of the atom of the molecule, and energy values for the most long-term transition of the electron. PC2 is most influenced by TE and the highest negative charge of the atom of the molecule.

In Fig. 2 presented with PCA, some of the sulfonamides sulfacarbamide, sulfacetamide, sulfamoxole, sulfanilamide, and sulfaguanidine in the case of structures in vacuo, and also sulfamoxole and sulfanilamide in the case of hydrated structures are out of the clusters formed by the rest of analyzed compounds.

Performed FA analysis for the molecules with the same calculation conditions coincides completely with the results obtained by PCA. Analyzing the molecules only with the use of HyperChem software, the following results were obtained: molecules in vacuo—FA1 49.66%, FA2 16.46%, and molecules in the aquatic environment—FA1 45.15%, FA2 17.40%.

Figure 3 with FA also shows some of the before-mentioned sulfonamides: sulfacarbamide, sulfacetamide, sulfamoxole, sulfanilamide, and sulfaguanidine in the case of both structures in vacuo and hydrated are out of the clusters formed by the rest of analyzed compounds.

In the next step, biological activity values were analyzed together with Gaussian and HyperChem descriptors (in vacuo from Gaussian, and in vacuo together within the aquatic environment from HyperChem). Since the values of biological activity were obtained for rather small collections of molecules (13–18 cases) for such small datasets, it was difficult to carry out external validation, so it was limited only to the internal validation leave-one-out together with progressive stepwise multiregression analysis; significant descriptors and equations were as follows:

Gaussian software in vacuo

$$\log 1/\text{MIC} = k_0 + 0.8469 \, \text{IsoPol} \, (\pm 0.1329), \tag{1}$$

$$R = 0.8469, R^2 = 0.7172, F = 40.5833,$$
$$s = 0.5481, p < 0.0001, n = 18, k_0 = 0,$$
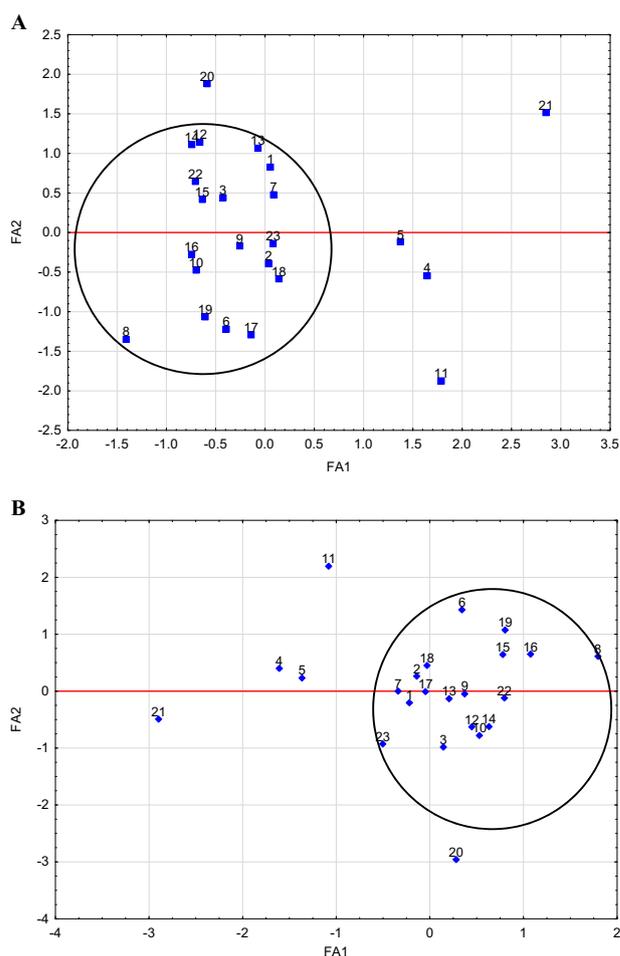
Fig. 3 Two-dimensional scatter plots of the scores first two factors obtained by FA structural parameters derived from the HyperChem quantum-chemical calculations from in vacuo **a** and hydrated **b** for selected antimicrobials (**a** FA1—49.66%, FA2—16.46%; **b** FA1—45.15%, FA2—17.40%)

$$\alpha = k_0 - 0.9914 \, \text{IsoPol} \, (\pm 0.1207) \\ + 0.4564 \, \text{MAX POS} (\pm 0.1207), \tag{2}$$

$$R = 0.9161, R^2 = 0.8392, F = 33.9178,$$
$$s = 0.4308, p < 0.0001, n = 16, k_0 = 0,$$

$$\beta = k_0 - 0.7094 \, \text{TE} \, (\pm 0.1884), \tag{3}$$

$$R = 0.7094, R^2 = 0.5032, F = 14.1808,$$
$$s = 0.7296, p < 0.0021, n = 16, k_0 = 0,$$

$$\text{PB} = k_0 + 0.9718 \, \text{IsoPol} \, (\pm 0.1737) \\ - 0.3911 \, \text{MAX POS} \, (\pm 0.1737), \tag{4}$$

$$R = 0.8708, R^2 = 0.7584, F = 15.6941,$$
$$s = 0.5385, p = 0.0008, n = 13, k_0 = 0,$$

HyperChem software in vacuo

$$\log 1/MIC = k_0 + 0.8435\,MeanPol\,(\pm 0.1343), \tag{5}$$

$$R = 0.8435, R^2 = 0.7115, F = 39.4591,$$
$$s = 0.5536, p < 0.0001, n = 18, k_0 = 0,$$

$$\alpha = k_0 - 0.8083\,MeanPol\,(\pm 0.1574) \tag{6}$$

$$R = 0.8083, R^2 = 0.6534, F = 26.3879,$$
$$s = 0.6094, p = 0.0002, n = 16, k_0 = 0,$$

$$\beta = k_0 - 0.7287\,DELTA\_Q\,(\pm 0.1830) \tag{7}$$

$$R = 0.7287, R^2 = 0.5310, F = 15.8515,$$
$$s = 0.7089, p = 0.0013, n = 16, k_0 = 0$$

$$PB = k_0 - 0.4366EE(\pm 0.1890) + 0.3674E\_HOMO$$
$$(\pm 0.1226) + 0.4798HF(\pm 0.1892), \tag{8}$$

$$R = 0.9316, R^2 = 0.8678, F = 19.6992,$$
$$s = 0.4198, p = 0.0003, n = 13, k_0 = 0$$

HyperChem software aquatic environment

$$\log 1/MIC = k_0 + 0.8438\,MeanPol(\pm 0.1342), \tag{9}$$

$$R = 0.8438, R^2 = 0.7120, F = 39.5599,$$
$$s = 0.5532, p < 0.0001, n = 18, k_0 = 0,$$

$$\alpha = k_0 - 0.8111\,MeanPol\,(\pm 0.1563) \tag{10}$$

$$R = 0.8111, R^2 = 0.6579, F = 26.9258,$$
$$s = 0.6054, p = 0.0001, n = 16, k_0 = 0,$$

$$\beta = k_0 + 0.6256\,MeanPol\,(\pm 0.2085), \tag{11}$$

$$R = 0.6256, R^2 = 0.3914, F = 9.0023,$$
$$s = 0.8075, p = 0.0095, n = 16, k_0 = 0,$$

$$PB = k_0 - 0.7866EE(\pm 0.1429)$$
$$+ 0.3561E\_HOMO(\pm 0.1429), \tag{12}$$

$$R = 0.8931, R^2 = 0.7976, F = 19.7029,$$
$$s = 0.4928, p = 0.0003, n = 13, k_0 = 0,$$

Analyzing the quantum-chemical parameters obtained for the biological and pharmacokinetic parameter values in the case of Gaussian in vacuo, the most influence for log1/MIC is IsoPol, for α IsoPol and MAX_POS, and for β TE and for PB again IsoPol and MAX_POS. On the other hand, in the case of HyperChem statistically important in vacuo quantum-chemical descriptors, we can distinguish MeanPol

for log1/MIC and α, DELTA_Q for β and EE, and E_HOMO together with HF for PB, while in the aquatic environment, MeanPol for log1/MIC α and β and finally EE and E_HOMO for PB.

In the next step, so progressive stepwise multiregression analysis was performed, but with the use of a huge set of additional descriptors obtained by the professional software for the analyzed compounds with owned biological activity values and chromatographic retention data. Model equations for statistically significant descriptors are presented in the below set of derived equations:

$$\log 1/MIC = k_0 + 0.9183CMC - 80\,(\pm 0.0990), \tag{13}$$

$$R = 0.9183, R^2 = 0.8433, F = 86.1322,$$
$$s = 0.4080, p < 0.0001, n = 18, k_0 = 0,$$

$$\alpha = k_0 + 2.6386\,SpMAD\_B\,(s)\,(\pm 0.3246) - 1.2234$$
$$SpMAD\_EA\,(dm)\,(\pm 0.2219) + 0.6877Wi\_G/D\,(\pm 0.1730), \tag{14}$$

$$R = 0.9720, R^2 = 0.9448, F = 68.3988,$$
$$s = 0.2628, p < 0.0001, n = 16, k_0 = 0,$$

$$\beta = k_0 - 0.8851\,Eig15\_AEA(dm)(\pm 0.1143) - 0.4186$$
$$H6i\,(\pm 0.1008) + 0.3329\,Eig02\_AEA(ed)(\pm 0.1092), \tag{15}$$

$$R = 0.9569, R^2 = 0.9157, F = 43.4483,$$
$$s = 0.3246, p < 0.0001, n = 16, k_0 = 0,$$

$$PB = k_0 - 0.7673Mor30e\,(\pm 0.1060)$$
$$+ 0.2720F09\,[C-N]\,(\pm 0.1060), \tag{16}$$

$$R = 0.9672, R^2 = 0.9355, F = 72.6197,$$
$$s = 0.2780, p < 0.0001, n = 13, k_0 = 0,$$

The full list of molecular descriptors obtained from Dragon software characterizing biological activity with their designations is presented in Table 3.

Performed predictions with the use of professional software and a wide range of molecular descriptors provide a more detailed information about the studied molecules. The obtained statistically significant molecular descriptors belong to different classes, but we can distinguish some of the common one's classes between them. In our opinion, it is difficult to indicate the most important equation between the proposed because the datasets are relatively small, and therefore we wanted to focus rather on the same block of descriptors appearing in the presented equations. Therefore, the most important group of descriptors characterizing biological activity of sulfonamides are the edge adjacency indices (SpMAD_EA(dm), Eig15_AEA, and Eig02_AEA

Table 3 List of statistically significant molecular descriptors characterizing examined biological activity in proposed QSAR/QSPR equations obtained from Dragon software

Descriptor	Full name	Block
CMC-80	Ghose–Viswanadhan–Wendoloski CMC drug-like index at 80%	Drug-like indices
SpMAD_B(s)	Spectral mean absolute deviation from Burden matrix weighted by I-state	2D matrix-based descriptors
SpMAD_EA(dm)	Spectral mean absolute deviation from edge adjacency mat. weighted by the dipole moment	Edge adjacency indices
Wi_G/D	Wiener-like index from distance/distance matrix	3D matrix-based descriptors
Eig15_AEA	Eigenvalue n. 15 from augmented edge adjacency mat. weighted by edge degree	Edge adjacency indices
H6i	H autocorrelation of lag 6/weighted by ionization potential	GETAWAY (GEometry, Topology, and Atom-Weights AssemblY) descriptors
Eig02_AEA(ed)	Eigenvalue n. 2 from augmented edge adjacency mat. weighted by edge degree	Edge adjacency indices
Mor30e	Signal 30/weighted by Sanderson electronegativity	3D-MoRSE (3D-Molecule Representation of Structures based on Electron diffraction) descriptors
F09[C–N]	The frequency of C–N at topological distance 9	2D atom pairs

3D three dimensional, *QSAR/QSPR* quantitative structure–activity/property relationship

(ed)) followed by 2D and 3D matrix-based descriptors (SpMAD_B(s), Wi_G/D) as appearing most often in proposed equations. Experimental equations confirmed the very important role of electronic properties of the molecules in antimicrobial activity of analyzed sulfonamides.

Finally, with possessed chromatographic retention parameters, also progressive stepwise multiregression analysis was performed. The chromatographic retention data parameters described with statistically significant descriptors from Gaussian, HyperChem, and Dragon software are presented in Table 4S. In the case of Gaussian, in vacuo statistically significant molecular descriptors characterizing chromatographic parameters the most often appear: IsoPol, ESE, and E_LUMO and finally MAX_POS and MAX_NEG. On the other hand, the most often appearing in vacuo descriptors from HyperChem are MeanPol, BE, and TE, while the most common descriptors from HyperChem in the aquatic environment also represent MeanPol, BE, and E_HOMO together with EL. By analyzing Dragon's statistically significant descriptors described with the retention parameters on the different chromatographic columns, we can select not only the same descriptor groups, but also exactly the same in several cases, between them are also again edge adjacency indices (SM06_EA(bo), SM08_EA (bo), Eig08_AEA(ed), Eig03_EA(ri), and Eig09_EA(ri)), 2D atom pairs descriptors (F04[C–O], F06[C–S], B06[C–S], and B08[C–O]), 3D-MoRSE descriptors (Mor26p, Mor12i, and Mor12u), Burden eigenvalues (SpMin1_Bh (s), SpMax2_Bh(p)), and finally GETAWAY and WHIM descriptors. All additional information pay attention to the role of the lipophilicity of analyzed sulfonamides in connection with atom fragment elements and simultaneously shape the geometry and van der Waals surface area of the molecules.

Conclusion

Based on the above discussion of the results that may be put forward, the following conclusion is presented. The set of analyzed molecules, for which optimization of the structures in the aquatic environment and in a vacuum was performed, parameters characterizing the classification are mostly compatible in all cases. In a set containing molecules for which optimization of the structure of isolated molecules was carried out and molecular parameters were calculated by the Hartree–Fock method, 6–31G with polarization functions d, p and in the presence of water molecules, where molecular parameters were calculated by the semiempirical method RM1, shows a classification partially consistent with the chemical structure and biological activity. By analyzing quantum-chemical descriptors characterizing biological activity values obtained from

HyperChem for the molecules in vacuo and in the aquatic environment, we can observe that they are comparable, but different from those for the Gaussian in vacuo molecules, while Dragon descriptors provide much more detailed information about the studied molecules of antimicrobial sulfonamides. Among the different parameters, the most important for the antimicrobial activity of sulfonamides confirmed repeated values of electronic property descriptors of analyzed molecules in proposed model equations characterizing both biological and retention parameters of sulfonamides. The above-presented method after extending the database with other amphoteric (zwitterionic) and monofunctional (acidic or alkaline) compounds could be used both for the initial classification of biologically relevant agents and could be included in the set of methods of QSAR analysis and design, as well as help in the verification of the hypothesis about functional dependencies between chromatographic or spectroscopic and nonempirical parameters. It seems advisable also to continue research in the extended database of molecules and their experimental values of pharmacological/physicochemical properties.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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