International Journal of Drug Discovery
ISSN: 0975-4423 & E-ISSN: 0975-914X, Volume 7, Issue 1, 2015, pp.-234-239.
Available online at http://www.bioinfopublication.org/jouarchive.php?opt=&jouid=BPJ0000224

RELATIONSHIP BETWEEN QUINOLONE STRUCTURE AND MINIMAL INHIBITORY CONCENTRATION OF BACTERIAL STRAINS

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Received: January 19, 2015; Revised: February 26, 2015; Accepted: March 03, 2015

Abstract- Quinolones are characterized by a broad spectrum of antimicrobial activity, favorable pharmacokinetic properties and low toxicity. The potential increase in resistance to quinolones, forces the manufacturers to carry out work on new drug substances. In a few works there have been attempts to find a correlation between the characteristics of the chemical structure and the value of minimal inhibitory concentration (MIC_{50}) of quinolones. Purpose of this study is to determine the relationship between physicochemical parameters of quinolones and the MIC_{50} values designated for *Haemophilus spp., Moraxella spp., Neisseria spp., Proteus vulgaris, Serratia spp., Shigella spp., Staphylococcus spp., Streptococcus spp., Yersinia spp.* Analysis of physicochemical parameters of selected drugs was made using MarvinSketch 5.11.5 (ChemAxon Ltd.) and QuickProp 3.1 software from Schrödinger package v 31207. MIC_{50} values were correlated with of the 51 physicochemical parameters calculated.

The leave-one-out (LOO) method was used for model cross-validation. The calculations were made in relation to the average value MIC_{50} 7 strains of bacteria Gram – and 2 strains of bacteria Gram +. A validation was carried out between proposed arithmetic expressions in relations to average values of MIC_{50} calculated only for these bacteria. It was shown that the analysis of the structure: MIC_{50} correlation, with regard to many bacterial strains requires the binding of many physicochemical structure parameters in the form of arithmetic expressions. Only a combination of physicochemical structure characteristics in the form of arithmetic expressions allows reflecting the complex interactions between the bacterial cell and drug molecules.

Keywords- *in silico*, MIC, QSAR, quinolones, validation.

Citation: Marczak M. and Grabowski T. (2015) Relationship between Quinolone Structure and Minimal Inhibitory Concentration of Bacterial Strains. International Journal of Drug Discovery, ISSN: 0975-4423 & E-ISSN: 0975-914X, Volume 7, Issue 1, pp.-234-239.

Introduction

Quinolones are characterized by a spectrum of antimicrobial activity, favorable pharmacokinetic properties and low toxicity [1,2]. The main mechanisms that cause increase of resistance in the case of quinolones are chromosomally-mediated quinolone resistance (CMQR) and plasmid-mediated quinolone resistance (PMQR).

In 2013 The European Food Safety Authority (EFSA) published a report on resistance to antibacterial agents of selected zoonotic bacteria and sentinel isolated in the European Union in 2011 [3]. The resistance of *Salmonella spp*. derived from poultry were tested in 16 countries. It was highest to the ciprofloxacin (an average of 28.7% of strains) and nalidixic acid (average 27.9%). In case of *S. enteritidis* 722 strains have been tested, where most of them were resistant to ciprofloxacin and nalidixic acid (approx. 30.8%). In the case of *Salmonella spp.* isolated from poultry meat resistance in the EU averaged 50.1% for ciprofloxacin and 44.8% for nalidixic acid. The data on *Campylobacter spp.* derived from people pointed to the largest percentage of strains resistant to among other things, to nalidixic acid 47.8% and ciprofloxacin 44.4%, in the case of C. *jejuni* resistance to nalidixic acid was 52.7% and 52.5% ciprofloxacin. Slightly higher levels were in the case of the *Campylobacter spp.* isolated (*C. jejuni, C. coli*) from poultry and for ciprofloxacin it was 57.2% and 55.5% for nalidixic acid. *C. coli* isolates derived from broilers in the majority were resistant to ciprofloxacin (76.6%) and nalidixic acid (70.2%). In the case of *C. coli* from pigs, resistance to ciprofloxacin fluctuated around 35.5% to nalidixic acid 32.8%, and for *C. jejuni* isolated from cattle resistance to nalidixic acid was 39.2% and to ciprofloxacin 38.8%. When it comes to data on *C. jejuni* isolated from poultry meat resistance to ciprofloxacin was 59.2% in the EU (highest in Poland, 90.2%) and 59.2% for nalidixic acid. In relations to *C. coli* isolated from poultry meat the resistance for ciprofloxacin was 77.7%, for nalidixic acid 72.2%. Data for E. coli isolated from poultry indicated for ciprofloxacin the resistance 40.5%, for nalidixic acid 72.2%. Data for *E. coli* isolated from poultry indicated the resistance to ciprofloxacin on average 40.5%, for *E. coli* isolated from poultry 4.8% for nalidixic acid. Based on this information, it was found that among strains of *C. coli* isolated from broilers and poultry a very high level of resistance in relation to the fluoroquinolone (ciprofloxacin) appeared (over 75% of isolates).

Regulatory Authorities (RA) clearly indicate the increasing threat of resistance to quinolones [4,5]. The potential increase in resistance to quinolones, as with other antimicrobial drugs forces the manufacturers to carry out work on new drug substances from this group as well [6,7]. In recent years, much work was devoted to study the relationship between the chemical structure of quinolones and their pharmacodynamic parameters [8-12]. In a few works there have been attempts to find a correlation between the characteristics of the chemical structure and the value of MIC_{50} of quinolones. However, in older works proposed models were not verified through comprehensive validation of the model [13,14]. Still, in relation to a number of quinolones relationships between physicochemical parameters and their antimicrobial activity expressed as MIC_{50} values within the individual bacterial strains has not been determined. Therefore the aim of the present study was to determine the relationship between physicochemical parameters of quinolones and the MIC_{50} values designated for *Haemophilus spp., Moraxella spp., Neisseria spp., Proteus vulgaris, Serratia spp., Shigella spp., Staphylococcus spp., Streptococcus spp., Yersinia spp.*

Materials and Methods

Drugs and Minimal Inhibitory Concentrations Selection

The values MIC_{50} were obtained from database KnowledgeBase, The Antimicrobial Index, Knowledgebase, version 1.8 and public domain [15-19]. Calculations were made for quinolones for which lowest MIC_{50} values were determined for all bacterial strains from tested group [Table-1]. Based on this criterion, cinafloxacin, gatifloxacin, gemifloxacin, moxifloxacin, sitafloxacin and trovafloxacin was selected for analysis.

Table 1- Minimum inhibitory concentrations (MIC_{50}) of six quinolones determined for nine bacterial strains: *Haemophilus spp., Moraxella spp., Neisseria spp., Proteus vulgaris, Serratia spp., Shigella spp., Staphylococcus spp., Streptococcus spp., Yersinia spp.* [15-19].

Substance	MIC_{50} [mg/mL]											
	Haemophullus spp.	Moraxella spp.	Neisseria spp.	Proteus vulgaris	Serratia spp.	Shigella spp.	Staphylococcus spp.	Streptococcus spp.	Yersinia spp.	GMean (RSD%)	Mean	Median
clinafloxacin	0.002	0.008	0.008	0.008	0.008	0.008	0.015	0.03	0.002	0.0073 (80.68)	0.0099	0.008
gatifloxacin	0.016	0.12	0.004	0.25	0.25	0.016	0.12	0.5	0.03	0.0621 (106.68)	0.1451	0.12
gemifloxacin	0.002	0.015	0.002	0.12	0.25	0.015	0.015	0.015	0.03	0.0178 (151.33)	0.0516	0.015
moxifloxacin	0.015	0.03	0.008	0.12	0.06	0.03	0.03	0.06	0.03	0.0326 (75.09)	0.0426	0.03
sitafloxacin	0.004	0.008	0.008	0.03	0.008	0.008	0.015	0.03	0.008	0.0106 (70.75)	0.0132	0.008
trovafloxacin	0.004	0.008	0.008	0.12	0.15	0.015	0.015	0.006	0.015	0.0165 (138.64)	0.0379	0.015

GMean – geometric mean; RSD% – percent of relative standard deviation; Mean – arithmetic mean; MIC_{50} – minimum inhibitory concentration required to inhibit growth of 50% of organisms.

In silico Calculations

Analysis of physicochemical parameters of selected drugs was preceded by the conversion of a structural chemical formula into a mol. file using MarvinSketch 5.11.5 (ChemAxon Ltd.). The converted data was used for calculation in QuickProp 3.1 software from Schrödinger package v 31207 [20,21]. QuickProp was run in the normal mode. Three-dimensional structures of compounds were prepared in LigPrep 2.2 (QuickProp, 2007). In case of the compounds that are chiral or undergo tautomerization, up to 32 stereoisomer calculations were generated for each compound or tautomer. The used software allowed for the calculations of 51 parameters [22].

Model Development

In the first step of the study, a search for direct correlation between chemical structure of, cinafloxacin, gatifloxacin, gemifloxacin, moxifloxacin, sitafloxacin and trovafloxacin and the MIC_{50} values of selected bacterial strains was conducted. At this stage, the MIC_{50} values were correlated with each of the 51 physicochemical parameters calculated. Following this in second step arithmetic expressions were constructed based on the values of all 51 of physicochemical parameters. The values of these expressions were correlated with the value of MIC_{50}, of tested drugs using a previously described method [22].

Statistical Analysis and Model Validation

A statistical analysis was performed utilizing Microsoft Office Excel® software. The linear correlation and regression analysis functions were used for the determination of a relationship between the mathematical model value and MIC_{50} of tested drugs. Correlations validated for MIC_{50} were confirmed by the Fisher's test (confidence interval 95%) and differences of $p<0.05$ were regarded as statistically significant. Finally, goodness of fit was evaluated based on MIC_{50}: arithmetic expression values. The coefficient of determination (R^2) of the observed versus predicted data was determined. The leave-one-out (LOO) method was used for model cross-validation [23,24]. Squared cross-validated correlation coefficient (Q^2) parameter and differences between Q^2 and R^2 were calculated as measure of the internal performance and model predictive ability. Q^2 was calculated according to the formula:

$$Q^2 = 1 - [\sum (Y_{obs} - Y)^2 / \sum (Y_{obs} - Y_m)^2]$$

where Y_{obs} – observed value for the i-*th* object, Y – value of the i-*th* object estimated by using a model, Y_m – average value of the validation set. Difference of ability between fitting and predictive ability was analyzed using difference between asymptotic squared cross-validated correlation coefficient (Q^2_{asym}) and Q^2 [25].

$$Q^2_{asym} = 1 - (1 - R^2) \times [n/(n - n_p)]^2$$

where R^2 – coefficient determination (Y_{obs} versus Y), n – number of the objects (internal validation set), n_p – number of parameters in final model. Validation acceptance criteria which have to be fulfilled by an optimized model were assumed on the level: $Q^2 \geq 0.65$, $R^2 \geq 0.85$, Q^2-$R^2 < 0.3$, Q^2_{asym}-$Q^2 > 0$ and 95% level of significance F test p-value < 0.05 [23-27]. Only a model that simultaneously meets all the criteria can be qualified as validated.

Results

The calculations were made in relation to the average value MIC_{50} (geometric - g, arithmetic - a, median - m) 7 strains of bacteria Gram– and 2 strains of bacteria Gram +. None of the individual physicochemical parameters was correlated with the mean value MIC_{50} determined on the basis of the analyzed nine bacterial strains. This concerned all, the arithmetic, geometric mean and median (g, a, m) [Table-2]. This began the creation of arithmetic expressions involving several features of the chemical structure at the same time and attempts to validate these expressions with the average value MIC_{50} (g, a, m) [Table-2]. Part of arithmetic expressions complied with the validation requirements [Table-3]. However, most expressions allowed for validation of the model only in relation to a geometric average MIC_{50}. None of the dependencies that met the criteria for validation in relation to the geometric mean of MIC_{50} met these criteria in relation to the arithmetic mean of MIC_{50}.

Table 2- Validation results in four validation configurations (A-D). - Model which not pass more than one validation criterion; g, a, m – model which meet validation criteria based on geometric, arithmetic or median of MIC_{50} value.

Arithmetic expression number	Validation set				
	All strains	Satphylococcus spp.	Moraxella spp.	Without G +	Without G -
	A	B	C	D	E
1	-	-	-	-	-
2	-	-	-	-	-
3	-	-	-	-	-
4	g	-	-	g	-
5	g	-	-	g	-
6	g	-	-	g	-
7	g, m	g, a, m	-	g	g, a, m
8	g, m	g, a, m	g, a, m	g	g, a, m

A – nine bacteria strains: *Haemophilus spp., Moraxella spp., Neisseria spp., Proteus vulgaris, Serratia spp., Shigella spp., Staphylococcus spp., Streptococcus spp., Yersinia spp.* was used for validation; B – one bacterial strain: *Staphylococcus spp.,* was used for validation; C – one bacterial strain: *Moraxella spp.,* was used for validation; D – six bacteria strains (without Gram positive bacteria): *Haemophilus spp., Moraxella spp., Neisseria spp., Proteus vulgaris, Serratia spp., Shigella spp., Yersinia spp.* was used for validation; E – two bacteria strains (without Gram negative bacteria): *Staphylococcus spp.,* and *Streptococcus spp.,* was used for validation.

Table 3- Validation parameters of arithmetic expressions, created from selected physicochemical parameters, and their correlation with MIC_{50} of nine bacteria strains (1–8 arithmetic expression): *Haemophilus spp., Moraxella spp., Neisseria spp., Proteus vulgaris, Serratia spp., Shigella spp., Staphylococcus spp., Streptococcus spp., Yersinia spp.*

No.	Q^2	R^2	Q^2-R^2	Q^2_{asym}-Q^2	SS	PRESS	F	p-value
Geometric mean of MIC_{50}								
1	0.8377	0.8046	0.0331	-0.0331	0.0025	0.00041	-	-
2	0.7741	0.6665	0.1084	-0.1084	0.0021	0.00048	-	-
3	0.8346	0.1103	0.7242	-0.7242	0.0202	0.00335	-	-
4	0.9288	0.9415	0.0127	0.0127	0.0032	0.00023	64.39	0.0013
5	0.948	0.9484	0.0006	0.0006	0.0034	0.00018	73.9	0.001
6	0.9424	0.9506	0.0082	0.0082	0.0034	0.00019	77.03	0.0009
7	0.9903	0.9932	0.0029	0.0029	0.0045	0.00004	580.67	0.000018
8	0.9953	0.9953	0.00001	0.00001	0.0048	0.00002	853.12	0.000008
Arithmetic mean of MIC_{50}								
1	0.7268	0.5714	0.1554	-0.1554	0.003387	0.012396	-	-
2	0.714	0.4254	0.2886	-0.2886	0.0037	0.012934	-	-
3	0.7335	0.0357	0.6978	-0.6978	0.020727	0.077787	-	-
4	0.7712	0.7777	0.0064	0.0064	0.003137	0.013713	-	-
5	0.8086	0.7922	0.0164	-0.0164	0.002825	0.014763	-	-
6	0.7903	0.7925	0.0022	0.0022	0.002988	0.014253	-	-
7	0.908	0.9068	0.0012	-0.0012	0.001643	0.017864	-	-
8	0.8973	0.8961	0.0012	-0.0012	0.001794	0.017467	-	-
Median of MIC_{50}								
1	0.7284	0.5913	0.1371	-0.1371	0.75117	2.76543	-	-
2	0.8529	0.4379	0.415	-0.415	0.00394	0.02679	-	-
3	0.8348	0.025	0.8099	-0.8099	0.02599	0.15736	-	-
4	0.8355	0.7989	0.0366	-0.0366	0.02493	0.15155	-	-
5	0.8384	0.8066	0.0317	-0.0317	0.02071	0.12811	-	-
6	0.8428	0.8131	0.0297	-0.0297	0.01484	0.09442	-	-
7	0.8248	0.9265	0.1017	0.1017	0.04486	0.25599	50.42	0.00207
8	0.7382	0.9258	0.1876	0.1876	0.61525	2.35025	49.91	0.00211

- Model which not pass more than one validation criterion; No. – Number of arithmetic expression [Table-2]; Q^2 — squared cross-validated correlation coefficient; Q^2_{asym} – asymptotic squared cross-validated correlation coefficient; R^2 – coefficient of determination; SS – sum of squares; PRESS – predicted residual sums of squares; F – Fischer test value.

In the presented work, LOO validation was carried out between proposed arithmetic expressions [Table-4] in relations to average values of MIC_{50} (g, a, m) calculated only for bacteria strains Gram+, and strains of Gram– bacteria [Table-2]. Models built on the basis of MIC_{50} designated on the basis of all strains, met the validation criteria in relation to individual strains as well. This was confirmed, however, only in relation to MIC_{50} *Staphylococcus spp*. and *Moraxella spp*. [Table-2]. Seven physicochemical parameters were used to build arithmetic expressions [Table-5]. Model 8 was considered to be the best fitted one [Table-3], [Table-4]. In this model, the highest value of F was reached, at very high values of the other validation parameters. This model was fitted to both, the average value of MIC_{50} of all analyzed strains [Fig-1](a-c) as well as to MIC_{50} of *Staphylococcus spp*. and *Moraxella spp*. [Fig-2](a&b).

Table 4- Arithmetic expression development

No.	Arithmetic expression	Validation criteria
1	LogDipole - HBD	not pass b, d
2	(LogDipole - HBD) X in56	not pass b, d
3	(LogDipole - HBD) + in56	not pass b, c, d
4	(LogDipole - HBD) / in56	pass validation
5	[LogSASA / (HBD-dip$^{2/v}$)] / (in56/LogDipole)	pass validation
6	[LogDipole/ (HBD-dip$^{2/v}$)] / in56	pass validation
7	[LogDipole/ (HBD-dip$^{2/v}$ X NandO)] / in56	pass validation
8	[LogDipole/ (HBD-dip$^{2/v}$) X NandO)] / in56 - QPLogP$_{o/w}$	pass validation

a – $Q^2 > 0.65$; b – $R^2 > 0.85$; c – Q^2-$R^2 < 0.3$; d – Q^2_{asym}-$Q^2 > 0$; dipole – computed dipole moment of the molecule; HBD – hydrogen bond donors; in56 – number of atoms in 5- or 6-membered rings; SASA – total solvent accessible surface area in square angstroms using a probe with a 1.4 Å radius; dip$^{2/V}$ – square of the dipole moment divided by the molecular volume; NandO – number of nitrogen and oxygen atoms; QPLogP$_{o/w}$ – predicted octanol/water partition coefficient.

Table 5- The values of the physicochemical parameters used in models that meet the validation criteria [Table-4].

Substance	Cinafloxacin	Gatifloxacin	Gemifloxacin	Moxifloxacin	Sitafloxacin	Trovafloxacin	M	SD	RSD%
Dipole	5.425	9.718	9.559	8.391	4.304	10.587	7.997	2.33	29.11
HBD	2	1	2	1	2	2	1.667	0.47	28.28
in56	15	16	15	19	14	19	16.333	1.97	12.07
SASA	571.14	606.77	676.79	629.02	623.84	639.17	624.45	31.97	5.12
dip$^{2/V}$	0.0295	0.0851	0.0775	0.0601	0.0167	0.0981	0.061	0.03	48.09
NandO	6	7	9	7	6	7	7	1	14.29
QPLogP$_{o/w}$	0.362	0.585	-0.271	0.979	1.206	1.097	0.66	0.51	77.11

Dipole – computed dipole moment of the molecule; HBD – hydrogen bond donors; in56 – number of atoms in 5- or 6-membered rings; SASA - total solvent accessible surface area in square angstroms using a probe with a 1.4 Å radius; dip$^{2/V}$ – square of the dipole moment divided by the molecular volume; NandO – number of nitrogen and oxygen atoms; QPLogP$_{o/w}$ – predicted octanol/water partition coefficient.

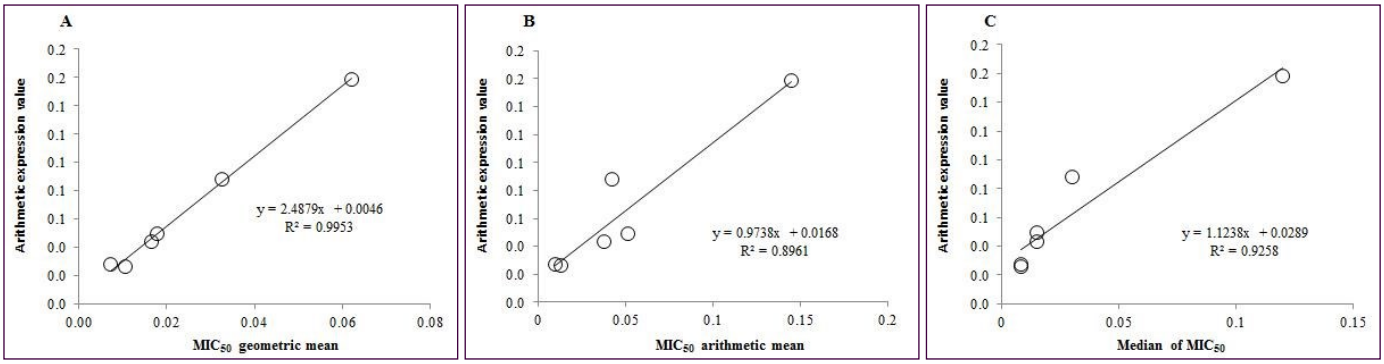

Fig. 1- Fitting of model 8 [Table-4] describing correlation between structure and geometric (A), arithmetic (B), and median (C), minimal inhibitory concentration of 50% population *Haemophilus spp., Moraxella spp., Neisseria spp., Proteus vulgaris, Serratia spp., Shigella spp., Staphylococcus spp., Streptococcus spp., Yersinia spp.* (MIC_{50}) in analyzed group of quinolones.

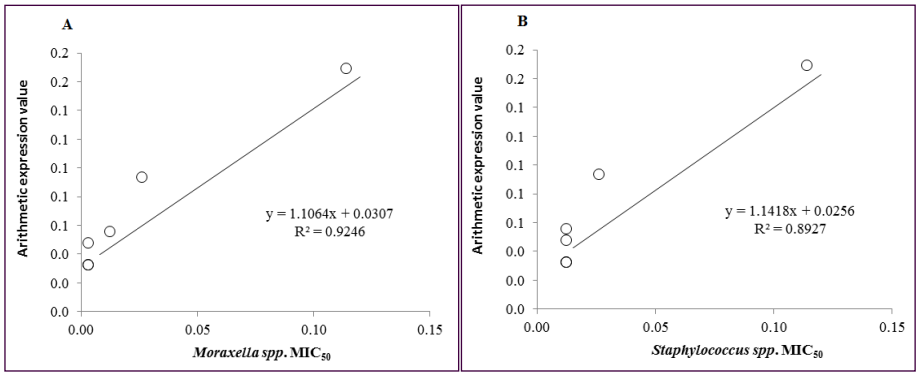

Fig. 2- Fitting of model 8 [Table-2] describing correlation between structure and minimal inhibitory concentration of 50% population *Moraxella spp.,* (A) *and Staphylococcus spp.,*(B) in analyzed group of quinolones.

Discussion

In this study, an attempt to correlate the chemical structure of some quinolones with MIC_{50} values was carried out. The model was verified during the validation procedure. The work was led bidirectionally, in the first stage the correlation of MIC_{50} structure was sought, based on the MIC_{50} average value calculated on the basis of selected strains of bacteria (g, a, m). At this stage, significant correlations were determined, that have been positively verified by validation using the LOO method. In the second step, the extent to which the proposed models meet the validation requirements in relation to selected bacterial strains or groups of bacteria. As a result of the carried out work, it was found that it is possible to determine the correlation and the validation of the model structure: MIC_{50}, both based on the average values calculated for a number of different strains simultaneously or individual or groups of strains (Gram+; Gram-). The validated on the basis of the average values models structure: MIC_{50} in the case of individual bacterial strains do not always allow for model revalidation. This means that the chemical structure parameters are related to the MIC_{50} value of different bacterial strains in different way, despite the same mechanism of drug action. This differentiation is best described by the arithmetic expression no 7, which in case of five validation groups (A-E) behaves in four different ways. Arithmetic expression illustrating the relationship between MIC_{50} and chemical structure features, in this case are formed by: computed dipole moment of the molecule (dipole), hydrogen bond donors (HBD), square of the dipole moment divided by the molecular volume ($dip^{2/V}$), number of nitrogen and oxygen atoms (NandO) as well as number of atoms in 5- or 6-membered rings (in56).These parameters have a direct link to the MIC_{50} value. However, it has been shown that their effect on MIC_{50} of analyzed quinolones is specific in relation to the strain of bacteria. In pharmacokinetic studies or PK / PD studies the effect of the drug is the result of absorption, distribution, metabolism and elimination. The results obtained in the present study represent the same relationships in relation to the bacterial cell. As the antibacterial effect illustrated by the MIC_{50} value results not only from the connection of the drug molecule to the molecular target inside the cell, but is also associated with various transport phenomena. As a result, as it was proved in the paper, the dependency between chemical structure features and the MIC_{50} value is specific for the bacterial strain. This fact is confirmed by Ghosh et al, who demonstrated that the relationship between inhibitory concentration with 50% effect (IC_{50}) in relation to the gyrase inhibition and a MIC_{50} is dependent on the bacterial strain and is not linear [28]. This means that the work devoted to the analysis of correlation between the binding's strength with the molecular target in the case of antimicrobial drugs describe only a portion of dependencies [29]. Analyses of this type do not include dependencies between drug's chemical structure, and the whole phenomena, which allow achieving the pharmacodynamic effect vivo (PD_{50}). This means that in order to provide a full picture of dependencies structure:PD_{50}, the dependencies structure:IC_{50} and structure:MIC_{50} must be verified separately, as they vary in character. The relationship between IC_{50} in relations to gyrase inhibition is not is not directly proportional to MIC_{50} [8]. This reasoning is confirmed by observations of the present work's authors. It is said that, the growth of *in vitro* activity positively correlated with chosen chemical substituents of quinolones molecules, is not always correlated with increasing effectiveness *in vivo* [29]. In relations to *Streptococcus sp*. the presented work confirmed earlier observations. The correlation between chemical structure of selected quinolones and the MIC_{50} value with regard to *Streptococcus pneumoniae* has also been confirmed by other authors [30]. The correlation between chosen chemical structure parameters and MIC_{50} of chosen quinolones was also confirmed in the case of *Staphylococcus aureus*, *Bacillus subtillis* and *Escherichia coli* [31]. In this case the correlation of derivative Log(1/MIC) was studied and it was confirmed in relations to one parameter - highest occupied molecular orbital energy (HOMO). Ghosh et al., in their work, prove significant relationship between several physicochemical characteristics of quinolones' structure and MIC_{50} for *Mycobacterium fortuitum* and *Mycobacterium smegmatis* [28]. However, these results have not been verified by the validation of the model.

The method that was used in present study has previously been successfully used for analysis of relationship between tetracyclines' structure and MIC and other drug safety related studies [22,32-34].

The present study shows that the analysis of the structure: MIC50 correlation, with regard to many bacterial strains requires the binding of many physicochemical structure parameters in the form of arithmetic expressions. Only a combination of physicochemical structure characteristics in the form of arithmetic expressions allows reflecting the complex interactions between the bacterial cell and drug molecules. The presented models were verified by LOO validation. The influence of creating MIC derivative (arithmetic, geometric, median) on model evaluation within the selected strains of bacteria and in the whole analyzed group was verified. A new method of studying the relationship between the pharmacodynamic features of the drug and chemical structure of the drug was presented. The presented method can be used in the detection phase of new antimicrobial drugs, and selection of potential drug candidates.

Conflict of Interest: Authors declare no conflict of interest.

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