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ORIGINAL PAPER

Factor analysis of microbiological activity data and structural parameters of antibacterial quinolones

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Abstract Factor analysis (FA) was performed on quinolone derivatives with antibacterial activity to model relationships between molecular descriptors and microbiological activities determined on five bacterial cell lines (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumoniae*). Molecular modeling studies were performed with the use of HyperChem software and MM+ molecular mechanics with the semi-empirical AM1 method. Factor analysis led to the extraction of two main factors, with the share of factor 1 amounting to about 76% and factor 2 to about 24% for all the parameters used in the statistical analysis. Moreover, FA results indicated that energy of orbitals lowest unoccupied molecular orbital, energy of ionization, electron affinity, electronegativity, maximum electron density, refraction and polarizability appeared to be descriptors important for the antibacterial activity of quinolones.

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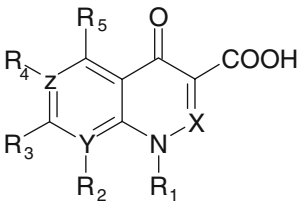
Keywords Antibacterial quinolines · Factor analysis · Molecular modeling descriptors

Introduction

Quinolones are derivatives of quinolo- or 1,8-naphthydrine-3-carboxylic acid, the characteristic feature of which is the presence of a carbonyl group in position 4 of the ring, and a substituted carboxylic group at the adjacent carbon atom in position 3. In addition to the compounds referred to above, the derivatives 4-cinnolone, 6,8-diazaquinolone and monocyclic 4-pyridine-3-carboxyl acid also belong to the quinolones group [1, 2].

The common precursor of compounds from the quinolones group, nalidixic acid, was synthesized in 1962. Generally, quinolone derivatives can be divided into three or even four generations [3–5]. The first generation includes compounds such as nalidixic acid, oxolinic acid, pipemidic or cinnoxacin, which do not contain a fluorine atom and affect only Gram-negative bacteria. However, flumequine, containing a fluorine atom and affecting Gram-negative bacteria, also belongs to this group [3]. The second generation, defined as fluoroquinolones, includes compounds with one or more fluoride substituents. This group includes compounds such as norfloxacin, ciprofloxacin, enoxacin, ofloxacin and lomefloxacin, which show high activity against Gram-negative bacteria and have a visible influence on Gram-positive bacteria [4, 5]. The third generation includes fluoroquilones, such as levofloxacin (levorotary isomer of ofloxacin), sparfloxacin, grepafloxacin, gatifloxacin, moxifloxacin and others, with comparable activity against Gram-negative and Gram-positive bacteria. The fourth generation consists of compounds such as trovafloxacin and alatrofloxacin, and is characterized by

Table 1 Chemical structure and antibacterial activity of quinolones studied



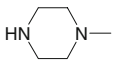
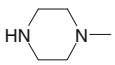
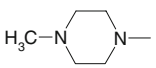
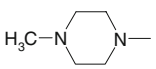
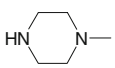
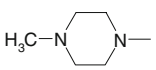
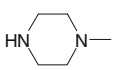
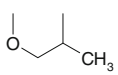
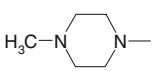
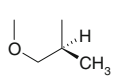
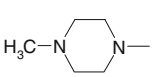
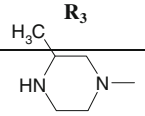
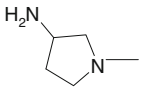
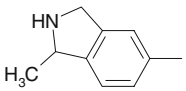
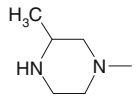
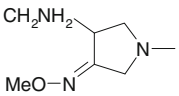
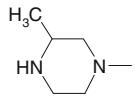
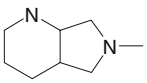
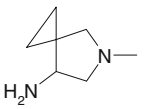
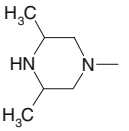
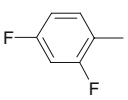
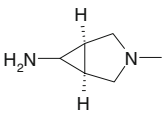
Compound	[a]Antibacterial activity					Chemical structure							
	E_COLI	K_PNEUM	P_AERUG	S_AUREUS	S_PNEUM	X	Y	Z	R_1	R_2	R_3	R_4	R_5
nalidixic acid	-1.433	-1.433	-2.634	-2.634	-2.634	C	N	C	CH_2CH_3	-	CH_3	H	H
piromidic acid	-2.239	-1.938	-2.540	-1.637	-2.540	C	N	N	CH_2CH_3	-		-	H
pipemidic acid	-1.010	-1.317	-1.317	-2.217	-2.518	C	N	N	CH_2CH_3	-		-	H
oxolinic acid	0.118	0.118	-0.058	-0.785	-2.581	C	C	C	CH_2CH_3	H			H
miloxacin	-0.182	0.119	-1.677	-1.379	-2.580	C	C	C	OCH_3	H			H
cinnoxacin	-2.280	-0.786	-2.581	-2.581	-2.581	N	C	C	CH_2CH_3	H			H
rosoxacin	0.169	-0.133	-1.331	-0.133	-1.629	C	C	C	CH_2CH_3	H		H	H
norfloxacin	0.504	0.805	0.203	-0.399	-0.700	C	C	C	CH_2CH_3	H		F	H
pefloxacin	0.523	0.824	-0.079	0.222	-0.380	C	C	C	CH_2CH_3	H		F	H
amifloxacin	1.126	0.223	-0.379	-0.689	-1.573	C	C	C	$NHCH_3$	H		F	H
ciprofloxacin	1.122	0.520	-0.082	-0.971	-0.684	C	C	C		H		F	H
fleroxacin	0.567	0.266	-0.637	-0.336	-1.232	C	C	C	CH_2CH_2F	F		F	H
enoxacin	0.506	0.506	-0.398	-0.986	-0.986	C	N	C	CH_2CH_3	-		F	H
ofloxacin	0.558	0.558	-0.044	-0.044	-0.345	C	C	C				F	H
levofloxacin	1.081	0.780	-0.141	0.479	-0.442	C	C	C				F	H

Table 1 (continued)

Compound	[(a)]Antibacterial activity					Chemical structure							
	E_COLI	K_PNEUM	P_AERUG	S_AUREUS	S_PNEUM	X	Y	Z	R_1	R_2	R_3	R_4	R_5
lomefloxacin	0.768	0.768	-0.454	-0.454	-1.056	C	C	C	CH_2CH_3	F		F	H
clinafloxacin	1.961	1.359	0.466	1.086	0.785	C	C	C		Cl		F	H
garenfloxacin	0.852	0.551	-0.370	1.454	0.852	C	C	C		$OCHF_2$		H	H
gatifloxacin	1.097	0.796	-0.426	0.796	0.177	C	C	C		OCH_3		F	H
gemifloxacin	1.687	1.113	0.192	1.113	0.812	C	N	C		-		F	H
grepafloxacin	1.352	0.777	0.158	0.777	0.158	C	C	C		H		F	CH_3
moxifloxacin	1.126	0.826	-0.697	1.126	0.507	C	C	C		OCH_3		F	H
sitafloxacin	1.710	1.436	0.499	1.436	1.136	C	C	C		Cl		F	H
sparfloxacin	1.418	1.418	-0.105	0.816	0.515	C	C	C		F		F	NH_2
trovafloxacin	1.415	1.142	-0.0800	0.841	0.841	C	N	C		-		F	H

[(a)] antibacterial (microbiological) activity data MIC (means the lowest concentration inhibiting the growth of microbes *in vitro*) was transformed to logarithm and expressed as log 1/MIC were E_COLI means log 1/MIC for *Escherichia coli*, K_PNEUM for *Klebsiella pneumoniae*, P_AERUG for *Pseudomonas aeruginosa*, S_AUREUS for *Staphylococcus aureus* and S_PNEUM for *Streptococcus pneumonia*, respectively.

good activity against Gram-negative and Gram-positive bacteria as well as quinolones of the third generation. Moreover, these compounds are additionally active against anaerobic bacteria [6].

The mechanism of action of quinolones, important for their antibacterial activity, depends on inhibition of the activity of bacterial DNA gyrase enzymes from the topoisomerases group [1]. Bacterial DNA gyrase fulfils numerous functions necessary for the correct functioning of DNA replication processes. It also participates in transcription of certain genes, repair of damaged genes, and in gene recombination. Moreover, in prokaryotic

Table 2 Values of molecular descriptors used in factor analysis

Compound		Molecular descriptors														
No.	Name	TE	BE	IAE	EE	CCE	HF	E_HOMO	E_LUMO	EG	IE	EA	EN	HARD	ED_MAX	ED_MIN
1	nalidixic acid	-113	-5.0	-108	-662	549	-73	-9.2	-0.70	8.5	8.7	-1.4	3.7	5.0	1.9	0.72
2	piromidic acid	-140	-6.2	-134	-921	781	-49	-9.0	-0.62	8.4	8.5	-1.4	3.5	4.9	1.9	0.72
3	pipemidic acid	-148	-6.5	-141	-999	851	-38	-9.2	-0.71	8.5	8.3	-1.5	3.4	4.9	1.9	0.72
4	oxolinic acid	-133	-5.3	-128	-791	658	-137	-8.9	-0.70	8.2	8.3	-1.4	3.4	4.8	1.9	0.72
5	miloxacin	-139	-5.0	-134	-799	661	-126	-9.1	-0.85	9.2	8.4	-1.6	3.4	5.0	1.9	0.74
6	cinnoxacin	-136	-5.1	-130	-795	659	-104	-9.0	-0.88	8.1	8.4	-1.8	3.3	5.1	1.9	0.74
7	rosoxacin	-138	-6.5	-131	-903	766	-43	-9.1	-0.91	8.2	8.6	-1.6	3.5	5.1	1.9	0.72
8	norfloxacin	-160	-6.9	-154	-1,095	934	-108	-8.8	-0.69	8.2	8.0	-1.4	3.3	4.7	2.0	0.73
9	pefloxacin	-166	-7.3	-159	-1,166	1,000	-104	-8.8	-0.68	8.1	7.8	-1.4	3.3	4.7	2.0	0.76
10	amifloxacin	-168	-7.1	-161	-1,176	1,008	-66	-8.8	-0.71	8.1	8.1	-1.5	3.3	4.8	2.0	0.72
11	ciprofloxacin	-165	-7.1	-158	-1,143	978	-73	-8.9	-0.65	8.1	8.0	-1.4	3.3	4.7	2.0	0.73
12	fleroxacin	-201	-7.3	-193	-1,379	1,179	-190	-8.9	-1.02	7.8	8.1	-1.7	3.2	4.9	2.0	0.72
13	enoxacin	-163	-6.7	-156	-1,094	932	-92	-9.0	-0.86	8.1	8.2	-1.5	3.3	4.9	2.0	0.72
14	ofloxacin	-182	-7.7	-175	-1,353	1,171	-132	-9.0	-0.83	8.2	7.9	-1.5	3.2	4.7	2.0	0.74
15	levofloxacin	-182	-7.7	-175	-1,355	1,173	-132	-9.0	-0.84	8.2	7.9	-1.5	3.2	4.7	2.0	0.74
16	lomefloxacin	-183	-7.3	-176	-1,284	1,101	-150	-9.0	-0.87	8.1	8.1	-1.6	3.2	4.8	2.0	0.72
17	clinafloxacin	-178	-7.1	-171	-1,247	1,068	-77	-9.1	-0.95	8.2	8.3	-1.6	3.4	4.9	2.0	0.72
18	garenfloxacin	-216	-9.0	-207	-1,686	1,470	-150	-9.0	-0.89	8.2	8.5	-1.8	3.3	5.2	1.9	0.76
19	gatifloxacin	-188	-8.1	-180	-1,4450	1,257	-108	-8.8	-0.74	8.1	8.0	-1.3	3.3	4.6	2.0	0.77
20	gemifloxacin	-198	-8.0	-190	-1,4450	1,247	-51	-8.9	-0.76	8.1	8.0	-1.4	3.3	4.7	1.9	0.72
21	grepafloxacin	-176	-8.0	-168	-1,334	1,157	-81	-8.8	-0.65	8.2	7.9	-1.4	3.3	4.6	2.0	0.74
22	moxifloxacin	-199	-8.8	-190	-1,594	1,395	-108	-8.9	-0.78	8.1	7.6	-1.4	3.1	4.5	2.0	0.76
23	sitafloxacin	-206	-7.7	-198	-1,497	1,291	-89	-9.2	-1.00	8.2	8.0	-1.7	3.2	4.8	2.0	0.76
24	sparfloxacin	-202	-8.3	-194	-1,540	1,338	-121	-8.5	-0.78	7.7	7.8	-1.5	3.2	4.7	2.0	0.73
25	trovafloxacin	-221	-8.0	-213	-1,618	1,397	-107	-9.4	-1.09	8.3	7.8	-1.7	3.1	4.8	2.0	0.74

cells, other enzymes, such as topoisomerase IV, are also responsible for DNA replication [7]. Generally, quinolones inhibit one of the above-mentioned enzymes, but some of them, such as clinafloxacin and sitafloxacin, can inhibit both of them [7], thus exerting more effective antibacterial activity.

Factor analysis (FA) is a chemometric technique based on principle component analysis (PCA)—a data processing method used to extract and visualize systematic patterns or trends in large data sets. The general idea of PCA is to reduce the dimensionality of the original multivariable data set by finding linear combinations of those variables that explain most of the variability within the set of data considered. By means of PCA, systematic information initially dispersed over a large matrix of input variables (often intercorrelated) is extracted and condensed into a few abstract variables. PCA involves a mathematical procedure that transforms the number of possibly correlated variables into a smaller number of uncorrelated variables called principal components. The first principal component accounts for as much of the variability in the data as possible, and each succeeding component accounts for as much of the remaining variability as possible. Usually a few principal components (PCs) are used to determine the abstract variable projection on the plane or in three dimensional space. Projections of data points ascribed to individual objects (here the antibacterial activity of quinolones) and to individual variables (here physicochemical descriptors) reflect mutual similarities and dissimilarities among them. In this way, basic information on the objects and variables can be exploited by the human mind, which naturally visualizes relationships only up those occurring in three dimensional space. PCA involves the calculation of the eigenvalues of a data covariance matrix, and the results of a PCA are usually discussed in terms of component scores and loadings. In other words, the independent variables applied are often mutually inter-correlated and, for this reason, inter-correlated data are unsuitable for multiple regression analysis and can be subjected to multivariate analysis as FA. In other words FA takes all the original parameters that are interrelated by simple

MAX_POS	MAX_NEG	DELTA_Q	X_DM	Y_DM	Z_DM	TDM	MP	EL	E MAX	OS_E MAX	SA	V	HE	LOG_ P	R	P
0.37	-0.41	0.78	-5.6	-0.04	0.98	5.6	135	3.7	5.4	0.71	420	683	-5.0	0.81	62	26
0.37	-0.41	0.78	-7.7	0.83	-0.27	7.8	172	3.9	4.6	0.97	494.	823	-4.9	1.08	78	29
0.37	-0.41	0.78	-6.9	0.28	-0.84	7.0	180	3.9	4.6	0.84	511	853	-7.7	0.19	81	31
0.37	-0.41	0.78	-6.0	-1.72	1.72	6.5	147	3.6	5.4	0.64	433	701	-9.6	-0.46	65	25
0.37	-0.39	0.76	-5.2	-0.84	1.68	5.5	142	3.6	5.0	0.56	426	683	-12	-0.18	62	24
0.39	-0.32	0.71	-5.6	-0.78	2.66	6.3	146	3.6	5.4	0.58	437	699	-12	1.70	63	24
0.37	-0.41	0.78	-4.9	-1.15	0.45	5.0	185	3.9	4.9	1.02	499	832	-8.2	2.08	82	32
0.37	-0.41	0.78	-6.3	-1.05	-0.02	6.4	186	3.8	4.4	0.91	515	869	-6.6	0.62	85	32
0.37	-0.41	0.78	-6.8	-1.00	3.17	7.6	195	3.7	4.5	0.89	541	916	-4.0	0.98	90	34
0.37	-0.40	0.78	-7.5	-0.46	1.79	7.8	193	3.7	4.4	0.88	532	904	-7.4	0.12	88	33
0.37	-0.41	0.78	-7.6	-0.50	0.61	7.6	194	3.7	4.5	0.92	532	902	-6.8	0.67	87	33
0.37	-0.40	0.77	-4.7	0.36	0.96	4.8	200	3.5	4.2	0.88	542	929	-4.1	0.94	90	34
0.37	-0.41	0.78	-6.2	0.40	0.23	6.2	184	3.7	4.6	0.70	518	872	-6.9	0.71	83	31
0.37	-0.41	0.78	-6.1	-3.11	2.40	7.2	203	3.9	4.3	0.50	553	948	-4.6	0.62	94	35
0.37	-0.41	0.78	-6.0	-2.95	2.62	7.2	203	3.9	4.3	0.51	555	949	-4.6	0.62	94	35
0.37	-0.40	0.78	-5.5	-0.43	0.08	5.5	198	3.6	4.2	0.88	541	925	-5.8	1.17	89	34
0.37	-0.40	0.77	-4.8	-1.31	-0.61	5.0	194	3.7	5.5	0.58	546	932	-8.4	0.91	92	35
0.37	-0.40	0.78	-4.8	2.11	3.14	6.1	247	3.9	4.6	0.73	635	1103	-7.8	2.78	110	42
0.37	-0.41	0.78	-5.6	-0.32	2.86	6.3	216	3.6	4.3	0.85	571	1000	-6.2	0.83	98	37
0.37	-0.40	0.78	-7.2	0.63	-0.25	7.3	226	3.7	4.6	0.90	618	1051	-11	1.20	99	37
0.37	-0.41	0.78	-5.2	-0.78	1.30	5.4	209	3.8	4.5	0.72	573	983	-5.2	1.55	97	37
0.37	-0.41	0.78	-7.6	-2.09	1.72	8.1	228	3.7	5.0	0.70	602	1058	-5.8	0.96	105	40
0.37	-0.40	0.77	-5.9	-0.08	2.17	6.3	210	3.9	6.0	0.38	573	1008	-7.5	1.29	98	38
0.38	-0.40	0.78	-2.4	0.80	0.95	2.7	220	3.4	5.6	0.56	599	1035	-7.4	0.86	101	38
0.37	-0.40	0.77	-4.5	-0.29	1.64	4.8	227	4.1	4.4	0.62	576	1009	-7.6	1.80	101	38

or multiple correlations, and combines them linearly to two orthogonal PCs (factors).

The goal of this study was to determine the relationship between the microbiological activity of antibacterial quinolones and their chemical structures, characterized by molecular descriptors and obtained by molecular modeling calculations applying FA methods.

Materials and methods

Microbiological activity data

The following antibacterial quinolones were investigated: nalidixic acid (**1**), piromidic acid (**2**), pipemidic acid (**3**), oxolinic acid (**4**), miloxacin (**5**), cinnoxacin (**6**), rosoxacin (**7**), norfloxacin (**8**), pefloxacin (**9**), amifloxacin (**10**), ciprofloxacin (**11**), fleroxacin (**12**), enoxacin (**13**), ofloxacin (**14**), levofloxacin (**15**), lomefloxacin (**16**), clinafloxacin (**17**), garenfloxacin (**18**), gatifloxacin (**19**), gemifloxacin (**20**), grepafloxacin (**21**), moxifloxacin (**22**), sitafloxacin (**23**), sparfloxacin (**24**), trovafloxacin (**25**; Table 1). Data regarding microbiological activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumoniae* were taken from the literature [1, 7–13] and expressed as log 1/MIC, where MIC (microbial inhibiting concentration) is the lowest concentration (in μmol dm^{-3}) inhibiting the growth of microbes in vitro.

The symbols assumed in this work for particular log 1/MIC values were derived from the names of the corresponding microbes, i.e. E_COLI means log 1/MIC for *Escherichia coli*, K_PNEUM for *Klebsiella pneumoniae*, P_AERUG for *Pseudomonas aeruginosa*, S_AUREUS for *Staphylococcus aureus* and S_PNEUM means log 1/MIC for *Streptococcus pneumoniae*.

Structural parameters

The structures of the tested compounds were studied by molecular modeling with the use of HyperChem 7.5 software (HyperCube, Gainesville, FL). The structures of the com-

pounds were firstly pre-optimized geometrically with the molecular mechanics force field procedure (with MM+ method) included in the HyperChem software. This allowed structures for further optimization steps to be prepared. The resulting structures were optimized further by means of a sophisticated, semi-empirical, quantum-based method (with the use of AM1 method) and applying the Polak-Ribiere algorithm with gradient limit of 0.01 kcal $Å^{-1}$.

The following molecular descriptors were considered among quantum and chemical indexes: total energy (TE), binding energy (BE), isolated atom energy (IAE), electron energy (EE), core-core energy (CCE), heat flow (HF), energy of the highest occupied molecular orbitals (E_HOMO) and energy of the lowest unoccupied molecular orbitals (E_LUMO), with the difference between HOMO and LUMO energies being referred to as the energy gap (EG); ionization energy (IE) potential and electron affinity (EA) were calculated as the difference between the heat flow of positive molecular ions and electrically neutral molecules (electron affinity) and were expressed in electron volts. The EG is defined as a value of the chemical hardness of the molecule connected with the polarizability of electrons. Electro-negativity (EN) was calculated as the average arithmetic IE and EA. "Hardness" of the molecules (HARD) was calculated according to Parr and Pearson [14] and Robles and Bartolotti [15], as half of the difference between IE and EA. For calculations of EN and HARD of the molecules, previously calculated values of IE and EA were used. Additionally, other authors [15] have used the value of electron density of atom orbitals from lowest to highest (ED_MAX and ED_MIN, respectively), the highest positive electron charge on the atoms (MAX_POS) and the highest negative electron charge on the atoms (MAX_NEG), the difference between the highest positive and negative charge (DELTA_Q), the distribution of dipolar moment along the x, y and z axes (X_DM, Y_DM and Z_DM, respectively), total dipolar moment (TDM), mean polarizability of molecules (in atom units), mean polarizability (MP), energy equal to the length of the wave of the most long-wave transfer of electrons, for which the value of oscillator force was different than zero (EL; the value of wave figures were converted to eV), and the value of the most intensive electron transfer (EMAX; the maximum value of oscillator force calculated using the AM1 method) as well as oscillator maximum force used for the transfer (OS_EMAX).

Moreover, additional parameters were calculated using the QSAR Properties Module of HyperChem 7.5 software. These include the following: surface area of the molecule available for solvent (SA), volume of molecule (V), hydratation energy (HE), calculated distribution coefficient logarithm (LOG_P); refraction (R) and polarizability (P).

Statistical analysis

The statistical (chemometric) QSAR analysis as FA was performed with the use of Statistica 5.1 software (StatSoft, Tulsa, OK).

Table 3 Factor analysis (FA) loadings by all structural parameters including also microbiological activity data

Structural parameter	Factor 1	Factor 2
TE	-0.9562[a]	-0.1832
BE	-0.9587[a]	0.1056
IAE	-0.9520[a]	-0.1941
EE	-0.9767[a]	-0.0872
CCE	0.9768[a]	0.0765
HF	-0.3084	-0.2856
E_HOMO	0.2359	-0.4783
E_LUMO	-0.3347	-0.7735[a]
EG	-0.5608	0.0926
IE	-0.7558[a]	0.3083
EA	-0.0793	-0.8752[a]
EN	-0.7866[a]	-0.1968
HARD	-0.5547	0.6388
ED_MAX	0.7495[a]	-0.1863
ED_MIN	0.5340	0.1328
MAX_POS	-0.0254	0.4833
MAX_NEG	0.2282	0.4311
DELTA_Q	0.3413	-0.6559
X_DM	0.2012	0.6467
Y_DM	0.0193	0.2463
Z_DM	0.2547	0.2464
TDM	-0.0973	-0.5717
MP	0.9496[a]	-0.0208
EL	0.0846	0.0485
EMAX	-0.2471	0.4186
OS_EMAX	-0.1687	-0.4948
SA	0.9422[a]	-0.0631
V	0.9566[a]	-0.0560
HE	0.2948	-0.4492
LOG_P	0.3708	0.5079
R	0.9621[a]	-0.0624
P	0.9547[a]	-0.0388
E_COLI	0.8383[a]	-0.1104
K_PNEUM	0.8234[a]	0.0542
P_AERUG	0.7723[a]	-0.2107
S_AUREUS	0.9063[a]	0.0457
S_PNEUM	0.9349[a]	0.0798

[a] Highest principal component (PC; factor) loadings among variables over 0.7

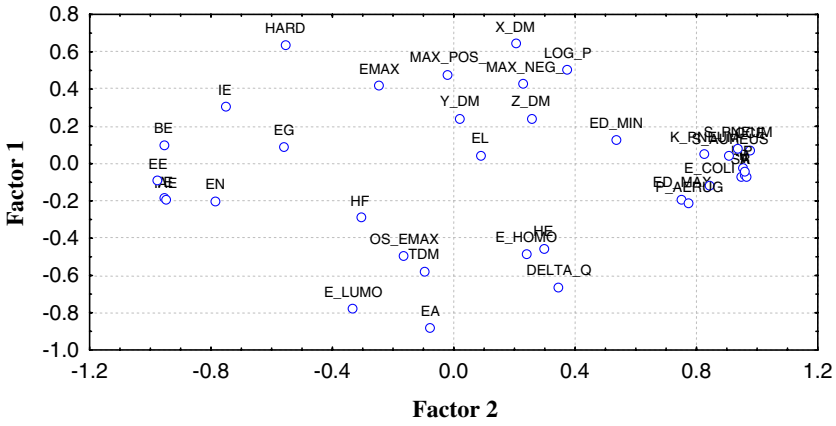


Fig. 1 Results of the factor analysis (FA) with all descriptors. Loading plot for Factor 1 and Factor 2

Results and discussion

The chemical structures of the considered compounds and their biological activity expressed as the log 1/MIC value are presented in Table 1. Values of all 32 structural parameters and the 25 considered compounds are presented in Table 2.

Table 4 FA scores of studied quinolones

No.	Compound	All data microbiological activity data[a]	
		Factor 1	Factor 2
1	nalidixic acid	-2.0395	-0.0180
2	piromidic acid	-1.3745	-0.8867
3	pipemidic acid	-1.0731	-0.5364
4	oxolinic acid	-1.2646	-0.4741
5	miloxacin	-1.5700	0.9113
6	cinnoxacin	-1.6495	2.3983
7	rosoxacin	-0.8273	0.6008
8	norfloxacin	-0.0960	-1.0487
9	pefloxacin	0.2564	-1.0517
10	amifloxacin	-0.0857	-0.9699
11	ciprofloxacin	-0.0278	-1.3634
12	fleroxacin	0.4110	0.5222
13	enoxacin	-0.2613	-0.1420
14	ofloxacin	0.5449	-0.4115
15	levofloxacin	0.5941	-0.3539
16	lomefloxacin	0.2532	0.0045
17	clinafloxacin	0.3248	0.7016
18	garenfloxacin	1.2146	1.6487
19	gatifloxacin	0.7565	-0.6944
20	gemifloxacin	0.7346	-0.7151
21	grepafloxacin	0.6301	-0.7406
22	moxifloxacin	1.1971	-0.8489
23	sitafloxacin	1.0284	1.1024
24	sparfloxacin	1.0726	0.6001
25	trovafloxacin	1.2512	1.7653

[a] FA performed for structural parameters including also microbiological activity data

Similarities and dissimilarities among the biological activity characteristics and physicochemical descriptors of the antibacterial quinolones studied were evaluated by FA. The results of FA provided the first two loadings (factor 1 and factor 2) of each variable, and their two-dimensional scatter plots obtained with the use of structural parameters including microbiological activity data are presented in Table 3 and Fig. 1. The highest PC (factor) loadings among the variables over 0.7 are presented in bold type. Factor analysis led to the extraction of two main factors from the analyzed group of parameters. In the set of all variables, the first factor accounted for about 76% of the variance, and the second for about 24%. These data indicated that the majority of the information contained in the original data matrix can be explained by two principal components, and can be interpreted that two principal components contain the whole information held previously in 37 original variables. Moreover, the factor 1 depends mostly on total energy (TE), binding energy (TE), isolated atom energy (IAE), electron energy (EE), core-core energy (CCE), ionization energy (IE), electro-negativity (EN), maximum density of electrons of atom orbitals (ED_MAX) and mean polarizability (MP), surface area of the molecule available for solvent (SA) and volume of molecule (V), refraction (R) and polarizability (P) and additionally for all log 1/MIC values; whereas factor 2 depends only on the energy of the lowest unoccupied molecular orbital (E_LUMO) and electron affinity energy (EA). The obtained data indicated that it is mainly energy of the molecule, molecular symmetry and topological properties that are important for microbiological activity of quinolones. Additionally, it is important to note that hydrophobic properties expressed as LOG_P (logarithm of theoretically calculated n-octanol-water partition coefficient) connected with transport and accumulation of these compounds in cells do not play an important role in the antibacterial activity of quinolones. Moreover, other calculated

physicochemical parameters, such as "hardness" of the molecule (HARD), and total dipole moment (TDM) and its distribution along x, y and z axes (X_DM, Y_DM and Z_DM respectively), hydratation energy (HE), electronic parameters as ED_MAX, ED_MIN, MAX_POS, MAX_NEG or DELTA_Q, and other parameters related to the energy of the molecule, such as HF, E_HOMO and EG have lower or no significance with regards to explaining the microbiological activity of quinolones. Thus one may suppose that parameters affecting the same factor to a greater extent will correlate better with each other, and, as a result, biological activity will depend more on parameters considerably affecting factor 1 rather than factor 2. The results presented are in accordance with previous observations made by Kaliszan and Ośmiałowski [16] for structural parameters: factor 1 represents properties mainly connected with molecular bulkiness, whereas factor 2 represents properties related to molecular polarity.

As the data mentioned above indicate, all information on the microbiological activity of quinolones (100 percent of total data variance) can be explained by the first two PCs. Therefore, particular quinolones can be compared on the basis of two PC scores (object) plots. Principal component solute scores calculated for all studied quinolones and their individual positions on the plane determined by the two factors axes and performed for structural parameters including microbiological activity data are presented in Table 4 and Fig. 2. All the studied compounds are characterized by an identical mechanism of biological action. Earlier studies [17, 18] established that compounds characterized by an identical mechanism of action in FA charts form clusters, e.g., classifications of compounds of α and β-adrenergic action, antagonists of histamine receptors H_1 and H_2 and psychotropic drugs. In the case of the quinolones studied here, their identical mechanism of action means that dissolution of individual compounds in the functions of factors 1 and 2 presented in the Fig. 2 reflect only the differences in antibacterial activity and in pharmacokinetics of respective compounds differing in chemical structure. Dissolution of this type was also observed for PABA and 11 antibacterial sulfonamides [19, 20].

The positions of particular quinolones on the plane determined by the axes of factors 1 and 2 obtained for structural parameters including microbiological activity data is presented in Fig. 2 and shows precisely the differentiation of the chemical structure of quinolones. Two main large clusters were observed, the first including quinolones of the first generation (**1**–**7**) with negative values of factor 2, and the second including the other 18 compounds (quinolones of higher generation**; 8**–**25**), with about zero and positive values, respectively. Moreover, values for factor 1 for quinolones of the first generation (**1**–**7**) are negative (**2**–**4**) or about zero/positive (**1**, **5**–**7**), whereas higher generation fluoroquinolones (**8**–**25**) have negative values (**8**–**11**, **19**–**22**) and about zero and positive values (**12**–**18**, **23**–**25**) of factor 1. Additionally, small cluster points of piromidic (**2**), pipemidic (**3**) and oxolinic (**4**) acids were located in the main cluster of quinolones of the first generation, whereas nalidixic acid (**1**), being a derivative of 1,8-naftiridine, and cinnoxacin (**6**), being a derivative of 4-cinnolon and having a dioxomethylene bridge in positions 6 and 7, are located furthest from these cluster points. On the other hand, the group of fluoroquinolones includes norfloxacin (**8**), amifloxacin (**10**) and ciprofloxacin (**11**), and the second group including pefloxacin (**9**), gemifloxacin (**20**) and grepafloxacin (**21**) form two small clusters within the main cluster of higher generation quinolones. Ofloxacin (**14**) (racemat) and levofloxacin (**15**) (left-handed derivative) points overlap each other, whereas points of enoxacin (**13**) and trovafloxacin (**25**), being a derivative of 1,8-naftiridine, clinafloxacin (**17**), which includes an atom of chlorine, and moxifloxacin (**22**), with a metoxylic group in position 8 and a octahydropirolopirydynyl substituent in position 7 are slightly distant. Another observation is that points of norfloxacin (**8**), amifloxacin (**10**), fleroxacin (**12**), lomefloxacin (**16**), garenfloxacin (**18**) and sitafloxacin (**23**), and points of pefloxacin (**9**),

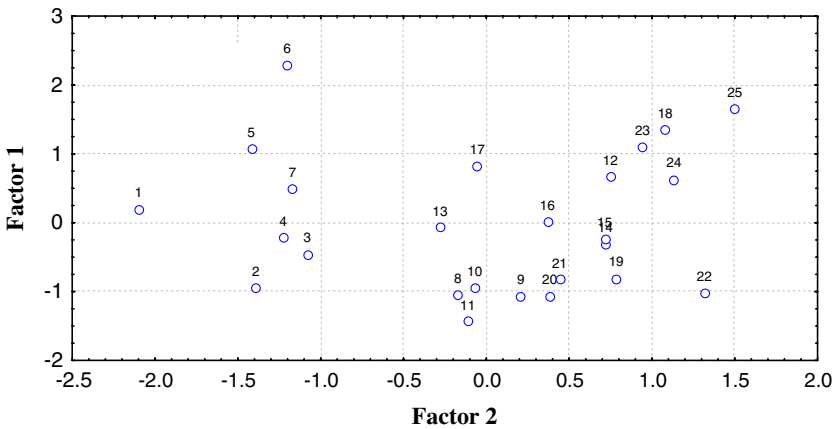


Fig. 2 Results of FA with all descriptors. Score plot for Factor 1 and Factor 2

ofloxacin (**14**), levofloxacin (**15**), gemifloxacin (**20**), grepafloxacin (**21**), sparfloxacin (**24**), trovafloxacin (**25**) are arranged in two straight lines. This initial assessment enabled us to observe that factor 1 is proportional to the force of antibacterial action; no unequivocal correlation of values of factor 2 with the force of action was observed.

Conclusions

Based on the above discussion of results, the following conclusions can be drawn.

Factor analysis leads us to distinguish two factors from the whole group of 37 parameters: the share of factor 1 amounts to about 76% and that of factor 2 to about 24% for all the parameters used in the statistical analysis.

Among all 37 parameters tested, quantum-chemical parameters (related to energy quantum-chemical parameters, energy of orbitals LUMO, energy of ionization, electron affinity, electronegativity, maximum electron density and medium polarizability), additive parameters (mainly area and capacity of particles and refraction and polarizability) and all parameters specifying microbiological activity have the highest influence on the value of factors. The data obtained indicate that it is mainly the energy of the molecule, the molecular symmetry and topological properties are important for microbiological activity of quinolones, and that all information on quinolones microbiological activity can be explained by the first two PCs.

Values of biological parameters depend mainly on the values of factor 1; dependence on factor 2 is statistically less important or only in particular cases (e.g., value log 1/MIC for *Pseudomonas aeruginosa*).

The proposed method, after extension of the database with other compounds both from within this group and with others of similar character (having groups of acid and basic character), might be used both for initial classification of biologically important elements and could be included in the set of methods of QSAR analysis. Factor analysis might help to specify correlations between chromatographic and non-empirical parameters or aid in the design of new predicted active molecules.

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