Artificial Neural Network Applied to Prediction of Fluorquinolone Antibacterial Activity by Topological Methods

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A new topological method that makes it possible to predict the properties of molecules on the basis of their chemical structures is applied in the present study to quinolone antimicrobial agents. This method uses neural networks in which training algorithms are used as well as different concepts and methods of artificial intelligence with a suitable set of topological descriptors. This makes it possible to determine the minimal inhibitory concentration (MIC) of quinolones. Analysis of the results shows that the experimental and calculated values are highly similar. It is possible to obtain a QSAR interpretation of the information contained in the network after the training has been carried out.

Introduction

Designing new drugs requires tools that make it possible to relate chemical structure with the properties of the molecule under study. The structure−activity relationships need to be established in such a way that the behavior of a series of molecules can be explained and, at the same time, the process can be inverted in order to obtain new structures that have the activity or property studied.

For this reason we have approached the question of how to depict the chemical structure from several angles. One of these is topology, by which the structure of the molecule is represented by a series of numbers, called indices, that contain information on the number and type of connections between the atoms that form the molecule.

A large number of quantitative structure−activity relationship (QSAR) studies have been reported in recent literature that use theoretical molecular descriptors in predicting the physicochemical, pharmacological, and toxicological properties of molecules.[1−9] The important common feature of all those descriptors is the independence of their numerical values on renumbering atoms in a chemical structure. To perform quantitative "structure−activity" and "structure−property" (QSPR) studies correctly, chemists have had to design a variety of molecular graph invariants.[10−13] Therefore, it becomes necessary to develop QSARs based on nonempirical parameters which can predict the biological properties for a homogeneous collection of chemicals so that such models are generally applicable.

We have chosen artificial neural networks[14−17] as a method for conducting such an analysis, because in the framework of this technique one can perceive relations between variables without having to specify their generic forms explicitly.[18,19] With this end in mind, in the current QSAR study we have examined 111 diverse antibacterial quinolones using differents types of nonempirical molecular descriptors.

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Materials and Methods

Representation of a chemical structure as a graph and reduction of the graph to various matrices is very familiar to many chemists, and this ground will therefore not be covered here. Any of the different matrices can be manipulated so as to produce local vertex invariants and from there a single number, usually referred to as a global invariant or a topological index,[20] and much effort has been expended in attempts to understand the properties of such indices. Two questions that seem to be particularly interesting are the relationship between a structure and its topological index and whether the topological index is related to the physical or chemical properties of a chemical.

Different topological indices say different things about a molecule. Some reflect the molecule's degree of branching, others its overall shape or bulk. The topological indices[21] can be regressed onto physicochemical and biological properties. There is a great deal of literature[22−24] on QSAR/QSPR studies, but both methods depend on some sort of regression which establishes a mathematical relationship between a molecular descriptor and either the (biological) activity or a (physicochemical) property. It is desirable to keep the number of descriptors to a minimum, and so selection of descriptors is an important step in the process. The end product of a QSAR study is a regression equation which relates the property (biological activity or physicochemical property) to the structure descriptors that were used.

It is undeniably useful for chemists to be able to predict properties and activity from a structure, whether by means of topological indices or some form of QSAR, but the ability to propose a structure with specific properties is a much more substantial goal, which is being sought by other means.

Taking into account all of the above, we chose a set of indices that provide a clear, simple description of molecular structure and can be used in studies on the relationships between this structure and its properties. We have developed original software that makes it possible to use the graphic formats frequently employed in chemistry to obtain the above-mentioned topological indices using the calculation sequence that appears in Figure 1.

The adjacency, distance, and substitution matrices yield, either directly or in conbination, a set of indices in the form of simple integers that relate to the molecular structure. We have chosen the molecule of ciprofloxacin (Figure 2) as an example of the calculation of indices via these matrices because it is one of the most characteristic ones in the quinolone group that we are examining and because its structure shows a large

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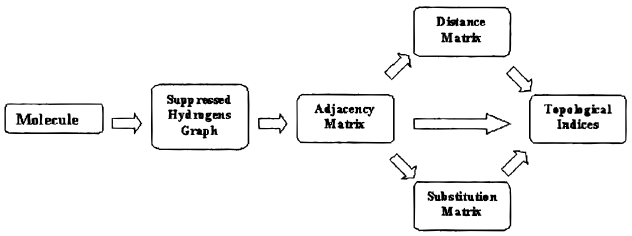


Figure 1. Calculation of topological indices.

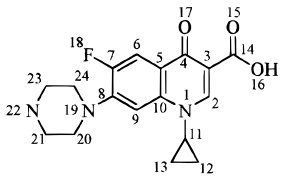


Figure 2. Chemical structure of ciprofloxacin.

number of topological features, like the presence of heteroatoms, double bonds, cyclic structures, etc.

The vertices in this structure were arbitrarily assigned numbers that correspond to the row and column designations of the matrix. An entry a_{ij} in the matrix has the value 1 when there is an edge between vertices i and j; otherwise it is 0:

$$(A)_{ij} = \begin{cases} a_{ij} & if \quad i \neq j \\ 0 & if \quad i = j \end{cases}$$

From the adjacency matrix we obtain the vertex degree vector, where δ_i for atom i is equal to the number of nonzero elements, in row i (or column i) in the adjacency matrix:

$$\delta_i = \sum_{j=1}^{n} a_{ij}$$

We define the modified adjacency matrix, where each element m_{ij} in the matrix has the value 1, 2, or 3 when the bond between vertices i and j is single, double, or triple, respectively; otherwise it is 0. The terms m_{ij} when $i = j$ are replaced by a code that indicates the type of atom:

$$(M)_{if} = \begin{cases} m_{ij} & if \quad i \neq j \\ C,N,O,... & if \quad i = j \end{cases}$$

The distance matrix is the length of the shortest path, d_{ij}, between the vertices in the graph:

$$(D)_{ij} = \begin{cases} d_{ij} & if \quad i \neq j \\ 0 & if \quad i = j \end{cases}$$

where D_{ij} is the number of steps in the shortest path (i.e. the minimum number of edges) in a graph beweeen vertices i and j.[25] Both matrices (modified adjacency and distance) are symmetrical with respect to the main diagonal and can be condensed into a single matrix. The upper half-matrix corresponds to the modified adjacency matrix, and the lower half-matrix corresponds to the distance matrix.

We have developed a set of algorithms that make it possible to calculate as many as 62 indices for each structure directly from this matrix. These indices not only fulfill the condition common to all topological indices of being graph invariants but also offer a second characteristic, which is that they are simple integers. This may constitute an advantage not only when we correlate the values of the indices with the physicochemical and pharmacological properties of a set of molecules (prediction and discrimination) but also when it comes to inverting the direction of the calculation and obtaining structures that have the mentioned properties and fulfill the topological requirements imposed by the functions found. This makes it possible to do a guided design.

Of the 62 indices the first 14 include simple information on the molecule such the number of carbon, nitrogen, oxygen, sulfur, fluorine, chlorine, and bromine atoms; the number of single, double, and triple bonds; and the number of primary through quaternary atoms. The remaining 48 indices include different topological information, such as the number of double bonds at the distance 1 or 2 and the minimum distance between pairs of atoms, counted as the number of bonds between atoms. The distances are measured with respect to each of the atoms other than the previously mentioned carbon atoms. In this way the number of indices assigned to each type of atom (depth) depends on the frequency with which it appears in the molecules with the pharmacological activity that we are studying.

Since the halogens are monovalent and distance 1 therefore coincides with the number of atoms of that element (this index is among the first 14 described), the assigning of distance indices begins from distance 2. The indices included in the so-called general group are the minimum distances between pairs of atoms without identifying the type of atom. The choice of 62 indices is arbitrary, and the number, type, and depth can vary depending on the criteria. The values described, however, seem to work well in pharmacological studies.

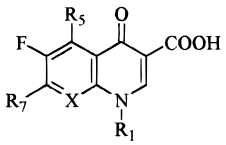
Once the whole set of indices to be used has been defined, the process of establishing the SARs begins. For this purpose we can use the traditional methods such as discriminant analysis and multilinear regression. These methods, however, are valid only if the relationship between the defined indices and the studied property is linear or if mathematical transformations have been applied to make it so. If this requirement is not fulfilled, as is usually the case with pharmacological properties, methods that make it possible to adequately establish these nonlinear relationships must be found. To solve this problem we decided to include artificial intelligence methods (neural networks) in the analysis that make it possible to improve the results obtained by the traditional multilinear regression methods.

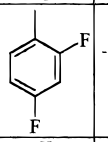
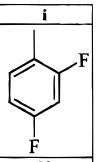
A different computer technique which is also modeled upon a biological process is the neural network.[26,27] This is an algorithm which makes decisions in a way which is similar to that in which the brain is thought to operate. The artificial neural network seeks to capitalize upon this design by providing a network of neurons, arranged in layers, which all contribute in some measure to complex decisions. In the typical neural net every connection between two neurons is associated with a weight, a positive or negative real number which multiplies the signal from the preceding neuron. The set of weights of the neural network from now on will be called the weights matrix. Each node accumulates and sums its various weighted inputs until some preset level, which depends on the nonlinear function employed, is reached, and at this point it fires and sends its signal to nodes in the next layer. The nonlinear function utilized is the hyperbolic tangent. The classification results achieved by the network are compared with known results, and then the weighting factors are corrected until the correct results are produced by the net. This is a supervised learning, and the correction process moves backward through every node of the net and is thus called "back-propagation".

We selected a total of 111 fluorquinolones with antibacterial activity and distributed them into nine groups according to the base structures presented in Table 1. The radicals R7 and R8 appear in Table 2.

The characteristic property of antibacterial drugs that we chose for this study was the minimum inhibitory concentration (MICs in μg/mL). The MIC for each compound is recorded in Table 2. The series of quinolones along with the reference agent ciprofloxacin were tested against *Escherichia coli* using standard microtitration techniques.[28,29] Moreover the MIC is known to be a difficult property to model. Since the methodology used to calculate the MIC involves assigning a value to each molecule depending on the inhibition limit observed, we distributed the molecules studied in three groups of MICs, ≤ 0.05, ≤ 0.10, and ≤ 0.20 μg/mL, and classified them with a + or − to show whether they belonged, according to their MIC values, to the groups (Table 2).

Table 1. Base Structure of Fluorquinolones



	a	b	c	d	e	f	g	h	i
R_1					- C_2H_5				
R_5	H	NH_2	H	H	H	H	H	H	H
X	C-R_8	C-R_8	C-R_8	C-R_8	C-R_8	C-R_8	C-R_8	N	N

Results and Discussion

The indices corresponding to the 111 quinolones under study were calculated using the methodology presented above. The molecules are classified in four groups according to their MIC values, obtained by applying the seriate dilutions method. The line corresponding to the indices of each molecule is called the molecule's spectrum and are presented schematically in Figure 3. The spectra of the four MIC groups are very similar because of the considerable homogeneity among the base structures of the groups studied, but this does not affect the capacity of the neural network to correctly classify the molecules being analyzed.

This group of 111 quinolones was divided into two parts: a training set (70% of the compounds) and a test set (30% of the compounds). The process of assigning the molecules to one of these sets was completely random and was performed 100 times in order to permit a statistical study that would give us an idea of the goodness of the method used.

Neural networks have also been applied by several authors[30−32] to study different physicochemical and pharmacological properties. In this experiment with a neural network, we chose prediction of MIC of quinolones because with this example it is possible to compare our results with those reported by other authors.[33−35]

The above-mentioned MIC classification provided the basis for designing a multilayer neural network made up of three subnetworks with two neurons in the hidden layer and one in the outer layer for each. For each MIC group the following correctness percentages were obtained: 100, 97.28, and 99.53 in the training set and 93.88, 82.36, and 87.99 in the test set for the MIC groups $\leq$0.05, $\leq$0.10, and $\leq$0.20 μg/mL, respectively.

It should be pointed out that the results obtained for the three groups of molecules are highly satisfactory, for the percentage of errors is low and they are concentrated in certain cases. On the other hand, most of the badly classified cases in any given group are correct in the other two, and none of the cases are incorrectly classified in all three groups.

If we analyze the cases with the highest percentage of errors in each group we find that in the MIC $\leq$ 0.05 μg/mL group only one case was erroneously classified 100% of the time (compound **4a**) and it was correctly classified 100% of the time in the other two groups. The experimental value of this molecule is 0.05 μg/mL, which marks the lower limit of this group.

In the same way we find that in the group with MIC $\leq$ 0.1 μg/mL, only one case is classified erroneously 100% of the time (compound **4h**). Again, the same case was correctly classified 100% of the time in the other two groups. The experimental value of this molecule is 0.2 μg/mL, which correponds to the upper limit of this group.

None of the cases in the group with MIC $\leq$ 0.2 μg/mL were classified incorrectly 100% of the time. Compound **7d** registered the highest percentage of errors (95%), but it was correctly classified in MIC $\leq$ 0.05 μg/mL 100% of the time and in MIC $\leq$ 0.1 μg/mL 81%. The experimental value of this molecule, 0.1 μg/mL, represents the lower limit of this group.

The behavior in these cases (the least favorable ones) is repeated in the other incorrectly classified cases. Therefore, the type of error that occurs when classifying by means of the neural network is similar to that obtained using the seriate dilution method, and this confirms the network's predictive validity. On the other hand, it is worth noting that the incorrectly classified cases in the training set correlate with a proportionally high percentage of errors in the test set.

As was to be expected, the largest percentage of errors is among the MIC $\leq$ 0.1 μg/mL intermediate group because this group is bounded by the other two, and the probability of error therefore increases. Despite this, more than 82% of the classifications are correct.

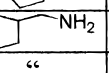
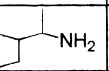
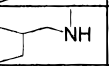
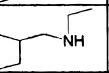
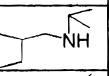
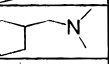
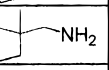
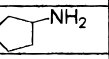
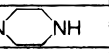
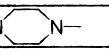
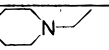
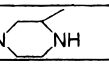
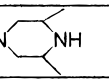
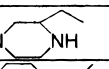
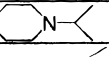
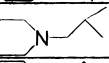
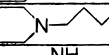
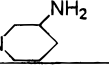
Although the range of concentrations used is very wide (from 0.006 to 3.1 μg/mL), the mean percentage of correct classifications in the test group is over 88%. Moreover, the highest percentage of successful classifications (93.88%) corresponds to the group of quinolones with the greatest antibacterial potency and, therefore, the most valuable ones from a pharmacological point of view. For this reason, if of the three subnetworks of the hidden layer we analyze only the one corresponding to the MIC $\leq$ 0.05 μg/mL group, this is sufficient to identify the molecules with an antibacterial activity equal to or greater than that of the reference drug, ciprofloxacin.

Analysis of the normalized contributions (Figure 4) obtained from the average of the 100 training and test cycles of each index makes a QSAR interpretation of the results possible if we take into account the fact that the final repercussion of each index is the product of its value and its normalized contribution (weights matrix). Therefore, a positive value in the neuron from the output layer indicates that the molecule belongs to this group and a negative value shows that it does not.

In view of the data presented in Figure 4 we can therefore say that indices **1**−**7** (number and atom type) demonstrate the importance of the presence of heteroatoms in the structures analyzed. Indices **2** (number of N atoms), **5** (number of F atoms), and **6** (number of Cl atoms) contribute in a positive way to the increase in potency, while **1** (number of C atoms) makes a negative contribution.

Indices **8**−**10** (number and bond type) contribute in a positive way, but index **8** (simple bond) has the greatest final repercussion, because of both its contribution and its value in itself. In other words, the presence of substituents without unsaturations has a more positive effect than unsaturated substituents (molecules **b** and **i**).

Table 2. Molecular Structures and MICs

Molecule	R7	R8	MIC (μg/ml)	≤ 0.05	≤ 0.1	≤ 0.2
1a		O-CH_2-CH_3	0.05	+	+	+
2a		H	0.05	+	+	+
3a	"	F	0.025	+	+	+
4a	"	O-CH_3	0.05	+	+	+
5a		F	0.013	+	+	+
6a		H	0.2	-	-	+
7a		H	0.1	-	+	+
8a	"	CF_3	0.4	-	-	-
9a	"	F	0.05	+	+	+
10a	"	O-CH_3	0.1	-	+	+
11a		H	0.4	-	-	-
12a		H	0.2	-	-	+
13a		H	0.1	-	+	+
14a	"	O-CH_3	0.1	-	+	+
15a	"	O-CH_2-CH_3	0.2	-	-	+
16a		H	0.05	+	+	+
17a	"	CF_3	0.1	-	+	+
18a	"	F	0.013	+	+	+
19a	"	Cl	0.013	+	+	+
20a	"	O-CH_3	0.025	+	+	+
21a		H	0.05	+	+	+
22a	"	O-CH_3	0.05	+	+	+
23a			0.05	+	+	+
24a	"	O-CH_3	0.1	-	+	+
25a		H	0.05	+	+	+
26a		H	0.05	+	+	+
27a	"	O-CH_3	0.05	+	+	+
28a	"	O-CH_2-CH_3	0.1	-	+	+
29a		H	0.05	+	+	+
30a	"	O-CH_3	0.1	-	+	+
31a		H	0.1	-	+	+
32a		H	0.1	-	+	+
33a		H	0.2	-	-	+
34a		H	0.1	-	+	+
35a		O-CH_3	0.1	-	+	+
36a	"	O-CH_2-CH_3	0.2	-	-	+

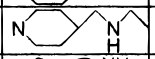
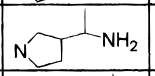
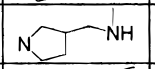
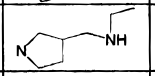
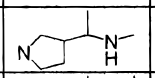
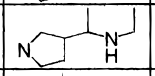
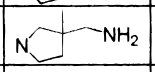
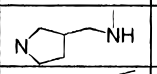
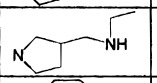
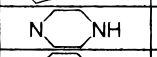
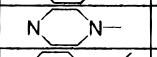
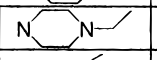
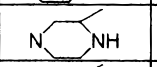
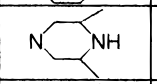
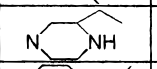
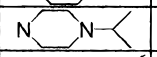
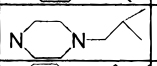
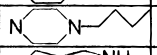
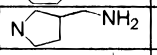
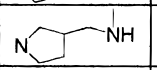
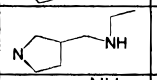
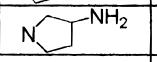
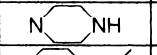
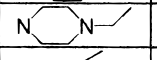
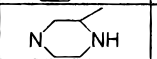
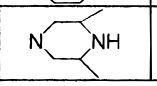
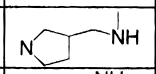
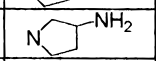
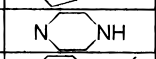
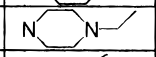
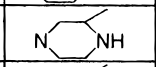
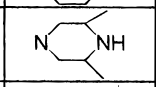
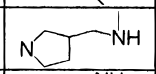
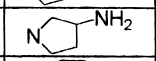
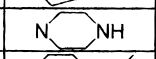
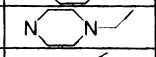
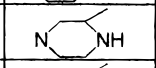
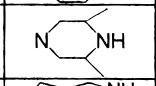
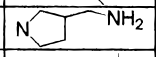
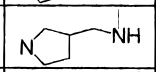
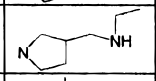
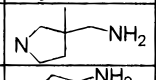
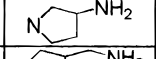
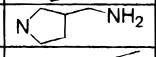
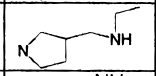
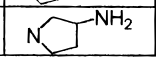
Molecule	R7	R8	MIC (μg/ml)	≤ 0.05	≤ 0.1	≤ 0.2
37a		H	0.4	-	-	-
38a	"	F	0.05	+	+	+
39a	"	Cl	0.1	-	+	+
40a	"	NH_2	0.4	-	-	-
41a	"	O-CH_3	0.2	-	-	+
42a	"	O-CH_2-CH_3	0.2	-	-	+
43a		O-CH_3	0.1	-	+	+
44a		O-CH_2-CH_3	0.8	-	-	-
1b		F	0.013	+	+	+
2b		H	0.025	+	+	+
3b		F	0.025	+	+	+
4b		H	0.1	-	+	+
5b	"	F	0.05	+	+	+
6b		H	0.1	-	+	+
7b		H	0.1	-	+	+
8b		F	0.2	-	-	+
9b	"	O-CH_3	0.1	-	+	+
10b	"	O-CH_2-CH_3	0.2	-	-	+
11b		H	0.013	+	+	+
12b	"	F	0.006	+	+	+
13b	"	O-CH_3	0.025	+	+	+
14b	"	O-CH_2-CH_3	0.05	+	+	+
15b		O-CH_3	0.2	-	-	+
16b		O-CH_3	0.1	-	+	+
17b	"	O-CH_2-CH_3	0.2	-	-	+
18b		F	0.05	+	+	+
19b	"	O-CH_3	0.1	-	+	+
20b		O-CH_3	0.1	-	+	+
1c		H	0.8	-	-	-
2c		H	0.4	-	-	-
3c		H	0.4	-	-	-
4c		H	0.8	-	-	-
5c		H	0.4	-	-	-
6c		H	0.4	-	-	-

Table 2 (Continued)

Molecule	R7	R8	MIC (μg/ml)	≤ 0.05	≤ 0.1	≤ 0.2
1d		H	0.2	-	-	+
2d		H	0.4	-	-	-
4d		H	0.1	-	+	+
5d		H	0.2	-	-	+
6d		H	0.4	-	-	-
7d		H	0.1	-	+	+
8d		H	0.4	-	-	-
9d		H	0.4	-	-	-
10d		H	0.8	-	-	-
11d		H	3.1	-	-	-
12d		H	0.8	-	-	-
1e		F	0.1	-	+	+
2e		H	3.1	-	-	-
3e		F	0.1	-	+	+
4e		H	0.4	-	-	-
5e	"	F	0.05	+	+	+
6e	"	O-CH_3	0.2	-	-	+
7e		H	0.1	-	+	+
8e		H	0.1	-	+	+
9e		H	0.2	-	-	+
10e		H	0.4	-	-	-

Molecule	R7	R8	MIC (μg/ml)	≤ 0.05	≤ 0.1	≤ 0.2
1f		H	3.1	-	-	-
2f		H	0.8	-	-	-
3f		H	0.8	-	-	-
4f		H	1.6	-	-	-
5f		H	0.8	-	-	-
6f		H	1.6	-	-	-
1g		H	0.4	-	-	-
2g		H	0.2	-	-	+
3g		H	0.2	-	-	+
4g		H	0.2	-	-	+
5g		H	0.1	-	+	+
6g		H	0.2	-	-	+
1h			0.05	+	+	+
2h			0.1	-	+	+
3h			0.1	-	+	+
4h			0.2	-	-	+
5h			0.013	+	+	+
1i			0.05	+	+	+
2i			0.2	-	-	+
3i			0.025	+	+	+

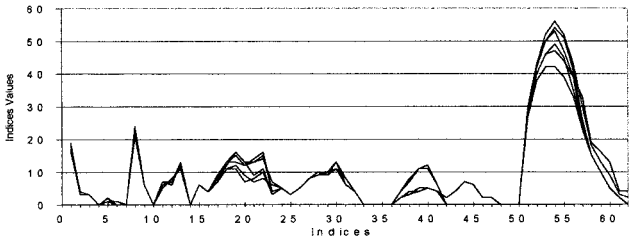


Figure 3. Molecular spectrum of some fluorquinolones studied.

Figure 4. Weights matrix with normalized contributions of each index.

Indices **11**−**14** (degree vertex) show a different type and degree of contribution. While index **13** (degree vertex 3) makes a positive contribution and also the largest one, the others contribute negatively. The most negative index is **11** (degree vertex 1). The molecules derived from **f** and **g**, which have the largest number of degree vertex (1), are less potent than the ones derived from structures **a** and **b**, which have a lower index value.

Indices **15** and **16** (conjugated double bonds) make a positive contribution and have a very similar value in all the molecules, for they are part of the base structure and show little variation from one to the other. Their presence does not, therefore, offer a differentiating character of the activity, for radicals R7 and R8 do not have unsaturations.

Indices **17**−**32** (distance from N or O) show a different type and degree of contribution. While indices **18**, **21**, **28,** and **30** do so in a markedly positive way, **17** and **22**−**24** are negative and the others are not very representative. With the exception of index **41**, indices **37**−**41** (distance from F) make a positive contribution.

Indices **51**−**62** (summatory of distance) show a different type and degree of contribution. While indices **51**

and **59** do so in a decidedly positive way, indices **52**, **53**, **55**, **56,** and **61** do so in a negative way. Index **52** (summatory of distance 2) has the greatest final repercussion, in terms of both its contribution and its value.

Conclusions

In this work our aim was to demonstrate the possibility of constructing a neural network for correlating the pharmacological properties of compounds directly with their structures. We use a novel set of topological descriptors applied to individual atoms and bonds in molecules. In other words, this methodology constitutes an alternative to the use of molecular descriptors in QSAR studies.

The results obtained confirm that the predictive model is quite adequate for the quinolone series studied, for with a simple neural network (two neurons in each subnetwork) a high percentage of correct classifications is achieved in the three groups of MIC values, especially in the group of the most potent molecules.

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Supporting Information Available: Experimental figures and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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