OBTENTION OF MINIMUM INHIBITORY CONCENTRATION PREDICTION EQUATIONS FOR ANTIBACTERIAL QUINOLONES VERSUS TWO GRAM-POSITIVE AND TWO GRAM-NEGATIVE PATHOGENIC BACTERIA

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The search of new molecules with therapeutic activity is a laborious process with an elevated economic cost. To find a new therapeutic activity for a compound which is provided with pharmacological and toxicological information mean an important saving of money and time which improve its pharmaceutical development as a new drug.[1] Among the different methods used for this purpose, molecular topology has showed to be a useful tool to find quantitative relationships between chemical structure and activity.[2]

In this work, a multilinear regression analysis has been carried out in order to look for functions capable of accurately predicting a series of biological properties of a group of quinolones, widely used nowadays because of their broad spectrum of activity, well tolerance profile and advantageous pharmacokinetic properties.[3]

The studied activities were minimum inhibitory concentration 50 against *Proteus vulgaris* (MIC_{50}Pv) and *Staphylococcus epidermidis* (MIC_{50}Se); and minimum inhibitory concentration 90 against *Clostridium perfringens* (MIC_{90}Cp) and *Haemophilus influenzae* (MIC_{90}Hi). We chose to target these bacterial species in this study since they are very common human pathogens. The structural description has been achieved through topological indices.

The results obtained clearly reveal the high efficiency of molecular topology for the prediction of these properties. Intercorrelation, Y-randomization and cross-validation by using leave-one-out test were also performed in order to assess the stability and the prediction ability of the functions selected.

The topological functions for the studied properties as well as their statistical parameters are shown in Tables 1 (Gram-positive bacteria) and 4 (Gram-negative bacteria). Calculated values with the prediction model have been compared with the ones obtained in the bibliography (Table 2 for *S. epidermidis*, Table 3 for *C. perfringens*, Table 5 for *P. vulgaris* and Table 6 for *H. influenzae*).

Table 1.- Prediction functions selected for the Gram-positive bacteria

Gram-positive bacteria	
$MIC_{50}Se = 33.7361 + 3.6953I_{Shann} - 4.20273S_{-OH} + 0.121029G^{v}_{4}$	N = 12; r = 0.9738; F = 48.89; SEE = 0.090874; SEE_{cv} = 0.151; p = 0.0000; r^2_a = 0.92889; r^2 = 0.94828; r^2_{cv} = 0.8498
$MIC_{90}Cp = 1.26153 - 2.0593S_{=C<} + 0.406247S_{-O-} - 0.724635V_4$	N = 16; r = 0.9408; F = 30.81; SEE = 0.29532; SEE_{cv} = 0.407; p = 0.0000; r^2_a = 0.85637; r^2 = 0.8851; r^2_{cv} = 0.7816

Table 2.- Randomly chosen prediction results obtained for the MIC_{50}Se activity (mg/L):

Compound	MIC_{50} exp	MIC_{50} calc
Fleroxacin	1.0000	0.9426
Gatifloxacin	0.1200	0.1131
Grepafloxacin	0.1200	0.1331
Levofloxacin	0.1537	0.1946
Norfloxacin	0.5000	0.5399
Temafloxacin	0.1850	0.1495
Sparfloxacin	0.0693	0.0971

Table 3.- Randomly chosen prediction results obtained for the MIC_{90}Cp activity (mg/L):

Compound	MIC_{90} exp	MIC_{90} calc
A-80556	0.5000	0.3844
ABT-492	0.0150	0.1827
BAY Y 3118	0.1250	0.2997
Ciprofloxacin	0.9375	0.7239
Fleroxacin	2.0000	2.0221
Grepafloxacin	0.7500	0.4865
Temafloxacin	0.5000	0.3014

Table 4.- Prediction functions selected for the Gram-negative bacteria

Gram-negative bacteria	
$MIC_{50}Pv = -1.24378 + 0.572422^{5}\chi^{v} + 0.0814509S_{aNa} - 0.051594S_{-O-}$	N = 15; r = 0.90135; F = 15.88; SEE = 0.101802; SEE_{cv} = 0.149; p = 0.0003; r^2_a = 0.76128; r^2 = 0.81243; r^2_{cv} = 0.5970
$MIC_{90}Hi = 0.767906 - 0.53818I_{Shann} - 0.0229907n_{hba} + 0.110345\Delta^{1}\chi$	N = 11; r = 0.94749; F = 20.48; SEE = 0.011471; SEE_{cv} = 0.017; p = 0.0008; r^2_a = 0.85392; r^2 = 0.89774; r^2_{cv} = 0.7671

Table 5.- Randomly chosen prediction results obtained for the MIC_{50}Pv activity (mg/L):

Compound	MIC_{50} exp	MIC_{50} calc
Enoxacin	0.2080	0.2224
Fleroxacin	0.0900	0.0878
Garenoxacin	0.2500	0.2164
Grepafloxacin	0.2500	0.2196
Moxifloxacin	0.5000	0.5156
Tosufloxacin	0.1200	0.1208
Sparfloxacin	0.2500	0.3010

Table 6.- Randomly chosen prediction results obtained for the MIC_{90}Hi activity (mg/L):

Compound	MIC_{90} exp	MIC_{90} calc
Ciprofloxacin	0.0870	0.0878
Clinafloxacin	0.0080	0.0062
Fleroxacin	0.0925	0.0947
Garenoxacin	0.0225	0.0356
Trovafloxacin	0.0265	0.0245
WIN57273	0.0600	0.0560
Sparfloxacin	0.0686	0.0634

The basis for the mathematical-topological models have been established since the analysis of the results obtained shows the validity of the topological model selected.

CONCLUSIONS

In this work, various models were developed in order to accurately predict different activities of antibacterial quinolones. Numerical descriptors used are easily calculated and contain the topological and structural information required for this purpose. Statistical studies of predictive capability confirmed that the selected regression models are effective in profiling major activities of antibacterial drugs. Thus, the obtained results have proven that the combined use of molecular topology along with multilinear regression analysis is very efficient in the prediction of microbiological properties.

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