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# Discrimination and selection of new potential antibacterial compounds using simple topological descriptors

Miguel Murcia-Soler [a], Facundo Pérez-Giménez [a,*], Francisco J. García-March [a], M. Teresa Salabert-Salvador [a], Wladimiro Díaz-Villanueva [b], Piedad Medina-Casamayor [a]

[a] *Department of Physical Chemistry, Faculty of Pharmacy, Universitat de València, Valencia, Spain*
[b] *Department of Computer Science and Electronics, Faculty of Physics, Universitat de València, Av. Vicent Andrés Estellés, s/n 46100 Burjassot, Valencia, Spain*

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**Abstract**

The aim of the work was to discriminate between antibacterial and non-antibacterial drugs by topological methods and to select new potential antibacterial agents from among new structures.

The method used for antibacterial activity selection was a linear discriminant analysis (LDA). It is possible to obtain a QSAR interpretation of the information contained in the discriminant function. We make use of the pharmacological distribution diagrams (PDDs) as a visualizing technique for the identification and selection of new antibacterial agents.


*Keywords:* Antibacterial activity; Compound classification; Linear discriminant analysis; Topological descriptors

## 1. Introduction

The prediction of the physicochemical, pharmacological, and toxicological properties of molecules in QSAR and QSPR can be computed from their molecular structure, encoded in a numerical form with the aid of various descriptors, such as graph theoretic and topological indices, and geometrical, electrostatic, and quantum-chemical descriptors [1–9].

One of the most active fields of research in contemporary chemical graph theory is the study of topological indices (TIs), numerical graph invariants that quantitatively characterize molecular structure, that can be used for describing and predicting physicochemical and/or pharmacologic properties of organic compounds [10–13].

Therefore, it becomes necessary to develop QSARs based on parameters which can predict the biological properties for a homogeneous collection of chemicals so that such models are generally applicable.

In Chemical Graph Theory, molecular structures are normally represented as hydrogen-suppressed graphs, whose vertices and edges act as atoms and covalent bonds, respectively. Graph-theoretical indices, also known as topological indices, are descriptors that characterize a molecular graph and are able to give account of their structural properties in order to obtain the connectivity functions used in discrimination and prediction studies [1]. They have shown their usefulness in classification analysis, and in general, in the modeling of biological activities [13,14].

We choose a group of antibacterials to demonstrate the discriminative ability of a group of simple topological descriptors in order to obtain a connectivity function that facilitates the molecular selection of new structures with potential antibacterial activity [14].

## 2. Methods

The calculation of the indices begins with the reduction of the molecule to the hydrogen-supressed skeleton or graph and reduction of this graph to several matrices.

We have designed software that make it possible to obtain the topological indices. The program expects an input file which can be in MDL Molfile format or SMILES code format and the output files are obtained in text format for further analysis.

In this structure were assigned numbers according to the sequence of atoms in SMILES code, that correspond to the

* Corresponding author. Tel.: +34-963-86-48-94; fax: +34-963-86-48-92.
*E-mail address:* facundo.perez@uv.es (F. Pérez-Giménez).

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row and column designations of the matrix. An entry $a_{ij}$ in the matrix has the value one when there is an edge between vertices $i$ and $j$; otherwise it is zero.

$$A_{ij} = \begin{cases} a_{ij} & \text{if } i \neq j \\ 0 & \text{if } i = j \end{cases} \quad (1)$$

From the adjacency matrix we obtain the vertex degree vector, where $d_i$ for atom $i$ is equal to the number of non-zero elements, in row $i$ (or column $i$) in the adjacency matrix.

$$\delta_i = \sum_{j=1}^{n} a_{ij} \quad (2)$$

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

$$M_{ij} = \begin{cases} m_{ij} & \text{if } i \neq j \\ \text{C, N, O, S, F, Cl, Br} & \text{if } i = j \end{cases} \quad (3)$$

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

$$D_{ij} = \begin{cases} d_{ij} & \text{if } i \neq j \\ 0 & \text{if } i = j \end{cases} \quad (4)$$

graph 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 $j$ [15]. Modified adjacency and distance matrices are symmetrical with respect to the main diagonal, and can be condensed into a combined matrix in which 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 [16,17]. 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 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 discriminant function. The above-mentioned methodology allows us to make the design and/or selection of new structures with the pharmacological activity studied.

Of the 62 indices the first 14 include simple information on the molecule such as the number and atom type, number and bond type and degree vertex. The remaining forty-eight 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 pharmacological activity that we are studying. The indices included in the so-called general distance group are the minimum distances between pairs of atoms without identifying the type of atom (Table 1).

Once the whole set of indices to be used has been defined, the process of establishing the structure-activity relationships begins. For this purpose we can use the traditional methods such as discriminant analysis and multilinear regression.

The linear discriminant analysis (LDA) was carried out by means of the BMDP 7 M statistical package [18], using the topological indices as independent variables [1]. LDA was used to select the parameters (pharmacological and/or structural) that identify the active or inactive character of the molecules. The analysis is carried out on two large groups of molecules, one with demonstrated antibacterial activity and the other inactive. The criteria for the selection of the best LDA equation were: comparison of the tabulated $F$-Snedecor and Wilk's $U$-statistical values; determination of the percentage of molecules correctly classified in each group; and prediction of the classification of molecules not included in the training process (cross-validation).

The discriminant functions are capable of describing pharmacological activity patterns and also non-activity patterns. In other words, this function points out not only the active drugs according to their distribution but also the inactive compounds. When applied to the discrimination of concrete pharmacological actions, we call them pharmacological distribution diagram (PDD) [19].

A PDD is a frequency distribution diagram of a dependent variable in which the ordinate represents the expectancies of this variable for every interval. The expectancies of this variable are defined as the probability that a compound will be active or inactive for a value of the discriminant function and are obtained by means of the expressions indicated in the text, in which 100 appears in the denominator to avoid dividing by zero.

$$E_{\mathrm{a}} = \frac{\text{Percentage of actives}}{\text{Percentage of inactives} + 100} \quad \text{(activity expectancy)}$$

$$E_{\mathrm{i}} = \frac{\text{Percentage of inactives}}{(\text{Percentage of actives} + 100)} \quad \text{(inactivity expectancy)}$$

The main advantage of these diagrams is that they make it possible to determine visually the intervals of property in which there is a maximum probability of finding new active compounds and a minimum of encountering inactive ones.

Once we have obtained the optimal discrimination conditions for classifying the antibacterial activity of a

Table 1
List and description of indices in output files

| Index | Description |
|---|---|
| Number and atom type indices | |
| 1 | Number of C atoms ($A^{C}$) |
| 2 | Number of N atoms ($A^{N}$) |
| 3 | Number of O atoms ($A^{O)}$ |
| 4 | Number of S atoms ($A^{S}$) |
| 5 | Number of F atoms ($A^{F}$) |
| 6 | Number of Cl atoms ($A^{Cl}$) |
| 7 | Number of Br atoms ($A^{Br}$) |
| Number and bond type indices | |
| 8 | Number of simple bonds ($B^{1}$) |
| 9 | Number of double bonds ($B^{2}$) |
| 10 | Number of triple bonds ($B^{3}$) |
| Degree vertex indices | |
| 11 | Number of atoms with degree vertex equal to one ($V^{1}$) |
| 12 | Number of atoms with degree vertex equal to two ($V^{2}$) |
| 13 | Number of atoms with degree vertex equal to three ($V^{3}$) |
| 14 | Number of atoms with degree vertex equal to four ($V^{4}$) |
| Conjugated double bonds indices | |
| 15 | Number of double bonds at distance 1 ($B^{D1}$) |
| 16 | Number of double bonds at distance 2 ($B^{D2}$) |
| Distance indices from each atom type | |
| 17 | Sum of atoms at distance 1 from N ($D^{N1}$) |
| 18 | Sum of atoms at distance 2 from N ($D^{N2}$) |
| 19 | Sum of atoms at distance 3 from N ($D^{N3}$) |
| 20 | Sum of atoms at distance 4 from N ($D^{N4}$) |
| 21 | Sum of atoms at distance 5 from N ($D^{N5}$) |
| 22 | Sum of atoms at distance 6 from N ($D^{N6}$) |
| 23 | Sum of atoms at distance 7 from N ($D^{N7}$) |
| 24 | Sum of atoms at distance 8 from N ($D^{N8}$) |
| 25 | Sum of atoms at distance 1 from O ($D^{O1}$) |
| 26 | Sum of atoms at distance 2 from O ($D^{O2}$) |
| 27 | Sum of atoms at distance 3 from O ($D^{O3}$) |
| 28 | Sum of atoms at distance 4 from O ($D^{O4}$) |
| 29 | Sum of atoms at distance 5 from O ($D^{O5}$) |
| 30 | Sum of atoms at distance 6 from O ($D^{O6}$) |
| 31 | Sum of atoms at distance 7 from O ($D^{O7}$) |
| 32 | Sum of atoms at distance 8 from O ($D^{O8}$) |
| 33 | Sum of atoms at distance 1 from S ($D^{S1}$) |
| 34 | Sum of atoms at distance 2 from S ($D^{S2}$) |
| 35 | Sum of atoms at distance 3 from S ($D^{S3}$) |
| 36 | Sum of atoms at distance 4 from S ($D^{S4}$) |
| 37 | Sum of atoms at distance 2 from F ($D^{F2}$) |
| 38 | Sum of atoms at distance 3 from F ($D^{F3}$) |
| 39 | Sum of atoms at distance 4 from F ($D^{F4}$) |
| 40 | Sum of atoms at distance 5 from F ($D^{F5}$) |
| 41 | Sum of atoms at distance 6 from F ($D^{F6}$) |
| 42 | Sum of atoms at distance 2 from Cl ($D^{Cl2}$) |
| 43 | Sum of atoms at distance 3 from Cl ($D^{Cl3}$) |
| 44 | Sum of atoms at distance 4 from Cl ($D^{Cl4}$) |
| 45 | Sum of atoms at distance 5 from Cl ($D^{Cl5}$) |
| 46 | Sum of atoms at distance 6 from Cl ($D^{Cl6}$) |
| 47 | Sum of atoms at distance 7 from Cl ($D^{Cl7}$) |
| 48 | Sum of atoms at distance 2 from Br ($D^{Br2}$) |
| 49 | Sum of atoms at distance 3 from Br ($D^{Br3}$) |
| 50 | Sum of atoms at distance 4 from Br ($D^{Br4}$) |
| General distance indices | |
| 51 | Sum of atoms at distance 1 ($D^{1}$) |
| 52 | Sum of atoms at distance 2 ($D^{2}$) |
| 53 | Sum of atoms at distance 3 ($D^{3}$) |
| 54 | Sum of atoms at distance 4 ($D^{4}$) |
| General distance indices | |
| 55 | Sum of atoms at distance 5 ($D^{5}$) |
| 56 | Sum of atoms at distance 6 ($D^{6}$) |
| 57 | Sum of atoms at distance 7 ($D^{7}$) |
| 58 | Sum of atoms at distance 8 ($D^{8}$) |
| 59 | Sum of atoms at distance 9 ($D^{9}$) |
| 60 | Sum of atoms at distance 10 ($D^{10}$) |
| 61 | Sum of atoms at distance 11 ($D^{11}$) |
| 62 | Sum of atoms at distance 12 ($D^{12}$) |

particular compound, the next step is to get new active compounds.

We selected a total of 241 molecules with antibacterial activity, classified by the Merck Index [20] within different therapeutic categories, belonging to different groups of antibiotics, such as aminoglycosides, amphenicols, β-lactams, tetracyclines, quinolones, sulfonamides, etc. and 731 molecules belonging to different therapeutic groups without this activity. The set was very carefully chosen in order to include as much structural heterogeneity as possible. In the case of antibacterials we had tried to take into account drugs acting through different mechanisms of action, including antibiotics, chemoterapics, bacteriostatic, and bactericides.

## 3. Results and discussion

The indices corresponding to the 241 antibacterial and 731 non-antibacterial compounds under study were calculated using the methodology presented above, and are presented schematically in Fig. 1. The line corresponding to the average indices values of active and inactive molecules, called the molecular spectrum.

The molecular spectrum shows a different profile on the antibacterial and non-antibacterial groups, with clearly differentiated zones for certain indices, like those referring to presence of heteroatoms (N and O), number of bonds and size of molecule, all of which have higher values in the antibacterial group.

This group of 972 molecules was divided into two parts: a discrimination set (70% of the compounds) and a test set (30% of the compounds) for both the active and inactive molecules. The process of assigning the molecules to one of these sets was completely random.

The best discrimination function was obtained with the variables $A^{N}$, $V^{1}$, $V^{2}$, $D^{N4}$, $D^{N7}$, $D^{N8}$, $D^{F4}$ and $D^{Cl4}$. Table 2 shows the discriminant function ($\Delta P$), obtained as the difference between the variables defining the groups of active and inactive molecules, together with the values for *F*-Snedecor and Wilk's *U*-statistical parameters used with each variable. Molecules with discriminant function values higher than 0.5 ($\Delta P > 0.5$) were classified as active, while

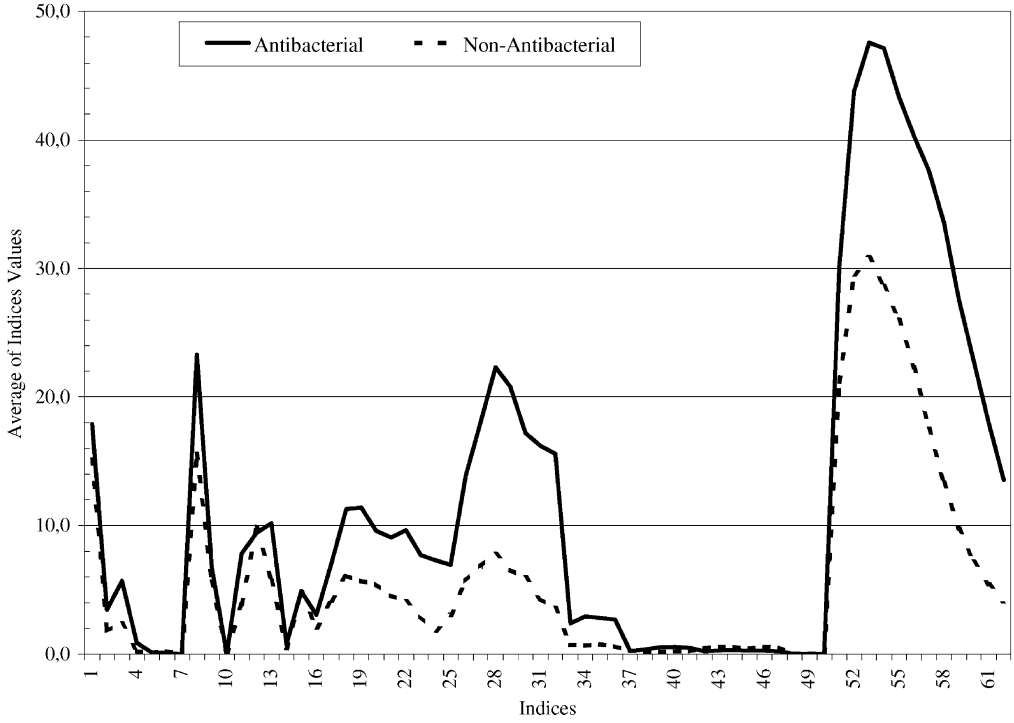


Fig. 1. Molecular spectrum of antibacterial and non-antibacterial compounds.

$\Delta P < 0$ corresponds to inactive molecules, and the compounds with $\Delta P$-values between 0 and 0.5 were classified as undetermined activity. These discriminant conditions imposed are intended to minimize the percentage of error, that is, to give the lowest possible number of false positives, although, a priori this may force us to discard a greater number of active compounds.

Table 3 shows the results obtained using 169 molecules with demonstrated antibacterial activity and 529 inactive molecules in the linear discriminant analysis (only the first 10 actives and inactives, the complete results are available as supplementary information (Tables 4 and 5 )). Misclassified compounds are those whose results were incorrectly predicted by the final LDA equation.

Table 2
Best obtained equation by linear discriminant analysis (LDA) applied to antibacterial activity

| Parameter | Coefficient | $F$ to remove | $U$-statistical |
|---|---|---|---|
| $A^{N}$ | 1.45357 | 10.3643 | 0.5435 |
| $V^{1}$ | 0.50274 | 45.6282 | 0.5807 |
| $V^{2}$ | −0.17579 | 111.4262 | 0.6188 |
| $D^{N4}$ | −0.33767 | 27.6137 | 0.5225 |
| $D^{N7}$ | −0.41569 | 21.3084 | 0.5633 |
| $D^{N8}$ | 0.72398 | 273.2860 | 0.7181 |
| $D^{F4}$ | 0.29523 | 11.7556 | 0.5138 |
| $D^{Cl4}$ | −0.32696 | 14.7239 | 0.5516 |
| Constant | −0.61929 | – | – |

Discriminant function $\Delta P = 1.45357\ A^{N} + 0.50274\ V^{1} - 0.17579\ V^{2} - 0.33767\ D^{N4} - 0.41569\ D^{N7} + 0.72398\ D^{N8} + 0.29523\ D^{F4} - 0.32696\ D^{Cl4} - 0.61929$.

Table 3
Results obtained by linear discriminant analysis, carried out with 169 different compounds with antibacterial activity and 529 different inactive compounds, containing data for the first 10 actives and inactives

| Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|
| (a) Active group[a] | | | |
| Acediasulfone | + | 0.60 | 52.06 |
| Amdinocillin pivoxil | + | 2.42 | 58.30 |
| Amikacin | + | 9.58 | 82.84 |
| Ampicillin | + | 2.29 | 57.84 |
| Apalcillin | + | 4.48 | 65.36 |
| Apramycin | + | 8.27 | 78.35 |
| Aspoxicillin | + | 9.13 | 81.30 |
| Azidamfenicol | + | 6.19 | 71.22 |
| Azlocillin | + | 3.51 | 62.04 |
| Aztreonam | + | 6.68 | 72.91 |
| (b) Inactive group[b] | | | |
| Alfentanil | + | 2.15 | 57.38 |
| Allylprodine | − | −4.11 | 35.91 |
| Alphaprodine | − | −3.42 | 38.27 |
| Benzylmorphine | − | −4.84 | 33.40 |
| Bezitramide | − | −3.01 | 39.67 |
| Butorphanol | − | −5.73 | 30.37 |
| Codeine | − | −3.28 | 38.74 |
| Desomorphine | − | −4.51 | 34.54 |
| Dextromoramide | − | −8.03 | 22.46 |
| Diampromide | − | −3.33 | 38.60 |

The complete results (supplementary information) are available in Tables 4 and 5.

[a] PA: probability of activity (%), undetermined (U) = 5.33%, false inactivity (−) = 20.71%, overall accuracy = 73.96%, adjusted accuracy = 78.13%.

[b] PA: probability of activity (%), undetermined (U) = 3.97%, false activity (+) = 5.10%, overall accuracy = 90.93%, adjusted accuracy = 94.69%.

Table 4
Supplementary information: results obtained by linear discriminant analysis, carried out with 169 different compounds with antibacterial activity and 529 different inactive compounds

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| (a) Active group[a] | | | | | | | |
| Acediasulfone | + | 0.60 | 52.06 | Cyclacillin | + | 1.90 | 56.51 |
| Amdinocillin pivoxil | + | 2.42 | 58.30 | Dapsone | U | 0.45 | 51.54 |
| Amikacin | + | 9.58 | 82.84 | Demeclocycline | + | 2.71 | 59.30 |
| Ampicillin | + | 2.29 | 57.84 | Dibekacin | + | 6.77 | 73.21 |
| Apalcillin | + | 4.48 | 65.36 | Dichloramine t | − | −2.34 | 41.98 |
| Apramycin | + | 8.27 | 78.35 | Difloxacin | + | 2.50 | 58.56 |
| Aspoxicillin | + | 9.13 | 81.30 | Dihydrostreptomycin | + | 14.58 | 100.00 |
| Azidamfenicol | + | 6.19 | 71.22 | Epicillin | + | 2.29 | 57.84 |
| Azlocillin | + | 3.51 | 62.04 | Erythromycin | + | 5.21 | 67.87 |
| Aztreonam | + | 6.68 | 72.91 | Fenbenicillin | − | −0.77 | 47.35 |
| Bacampicillin | + | 3.18 | 60.89 | Fleroxacin | + | 6.21 | 71.31 |
| Benzylsulfamide | − | −2.52 | 41.37 | Florfenicol | + | 2.11 | 57.25 |
| Biapenem | + | 3.66 | 62.55 | Floxacillin | − | −0.91 | 46.88 |
| Brodimoprim | + | 3.99 | 63.69 | Flumequine | − | −1.00 | 46.58 |
| Butirosin | + | 8.69 | 79.79 | Fortimicin b | + | 4.19 | 64.38 |
| Carbenicillin | − | −0.50 | 48.29 | Furaltadone | − | −0.60 | 47.93 |
| Carbomycin | + | 3.39 | 61.62 | Gentamicin | + | 8.88 | 80.45 |
| Carindacillin | − | −0.89 | 46.94 | Guamecycline | + | 9.44 | 82.37 |
| Cefaclor | − | −0.42 | 48.54 | Hexedine | − | −2.36 | 41.89 |
| Cefadroxil | + | 1.15 | 53.93 | Imipenem | + | 2.45 | 58.40 |
| Cefatrizine | + | 5.16 | 67.69 | Isepamicin | + | 11.36 | 88.96 |
| Cefazedone | + | 2.85 | 59.78 | Lenampicillin | + | 1.53 | 55.26 |
| Cefcapene pivoxil | + | 6.71 | 73.02 | Leucomycins | + | 2.88 | 59.89 |
| Cefdinir | + | 2.67 | 59.15 | Lomefloxacin | + | 5.41 | 68.56 |
| Cefetamet | + | 3.73 | 62.79 | Lymecycline | + | 5.83 | 69.98 |
| Cefixime | + | 1.51 | 55.19 | Mafenide | − | −2.59 | 41.11 |
| Cefodizime | + | 5.01 | 67.17 | Meclocycline | + | 2.64 | 59.04 |
| Cefonicid | + | 4.87 | 66.69 | Metampicillin | + | 1.36 | 54.65 |
| Ceforanide | + | 6.72 | 73.06 | 4(methylsulfamoyl)sulfanilanilide | + | 2.35 | 58.05 |
| Cefotaxime | + | 3.85 | 63.21 | Mezlocillin | + | 4.91 | 66.82 |
| Cefpiramide | + | 6.73 | 73.09 | Midecamycins | + | 2.53 | 58.69 |
| Cefpodoxime proxetil | + | 4.92 | 66.86 | Miloxacin | − | −3.07 | 39.46 |
| Cefroxadine | − | −0.05 | 49.84 | Minocycline | + | 5.93 | 70.35 |
| Cefteram | + | 6.30 | 71.60 | Miokamycin | + | 3.91 | 63.41 |
| Ceftibuten | + | 3.95 | 63.53 | Nadifloxacin | + | 0.68 | 52.32 |
| Ceftizoxime | + | 3.05 | 60.47 | Nafcillin sodium | − | −0.08 | 49.72 |
| Cefuroxime | + | 1.70 | 55.83 | Neomycin | + | 10.42 | 85.73 |
| Cefuzonam | + | 6.84 | 73.46 | Netilmicin | + | 8.44 | 78.95 |
| Cephalexin | + | 0.88 | 53.03 | Nifuradene | + | 0.67 | 52.31 |
| Cephaloglycin | + | 1.01 | 53.45 | Nifurfoline | − | −0.60 | 47.93 |
| Cephalothin | − | −0.55 | 48.10 | Nifurpirinol | U | 0.01 | 50.04 |
| Cephapirin sodium | U | 0.44 | 51.51 | Nifurprazine | + | 3.34 | 61.47 |
| Cephradine | + | 0.88 | 53.03 | Nitrofurantoin | + | 1.01 | 53.48 |
| Chloramphenicol | + | 1.73 | 55.95 | Norfloxacin | + | 2.11 | 57.23 |
| Chlortetracycline | + | 2.89 | 59.90 | Ofloxacin | + | 2.72 | 59.32 |
| Ciprofloxacin | + | 1.43 | 54.91 | Oxacillin | − | −1.47 | 44.97 |
| Clarithromycin | + | 5.76 | 69.75 | Oxytetracycline | + | 3.05 | 60.44 |
| Clinafloxacin | + | 0.97 | 53.33 | Panipenem | + | 3.51 | 62.05 |
| Clindamycin | − | −0.59 | 47.97 | Paromomycin | + | 7.85 | 76.92 |
| Clofoctol | − | −2.64 | 40.95 | Pazufloxacin | − | −0.54 | 48.14 |
| Clomocycline | + | 2.12 | 57.27 | Pefloxacin | + | 3.17 | 60.89 |
| Cloxacillin | − | −2.11 | 42.78 | Penicillin g | − | −0.17 | 49.40 |
| Penicillin n | + | 3.21 | 61.00 | Sulfalene | U | 0.30 | 51.04 |
| Penicillin v | − | −0.01 | 49.96 | Sulfaloxic acid | + | 1.15 | 53.93 |
| Phenethicillin potassium | + | 0.67 | 52.29 | Sulfameter | U | 0.04 | 50.15 |
| Phthalylsulfacetamide | + | 1.09 | 53.73 | Sulfamethazine | U | 0.22 | 50.77 |
| Pipacycline | + | 6.51 | 72.32 | Sulfamethizole | + | 1.33 | 54.57 |
| Piperacillin | + | 7.10 | 74.36 | Sulfamethoxazole | U | 0.32 | 51.11 |
| Piromidic acid | − | −2.08 | 42.85 | Sulfamethoxypyridazine | + | 0.64 | 52.20 |

Table 4 (*Continued*)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| Pivcefalexin | + | 3.18 | 60.89 | Sulfamidochrysoidine | − | −0.16 | 49.45 |
| Propicillin | − | −0.26 | 49.10 | Sulfamoxole | + | 0.66 | 52.28 |
| Quinacillin | + | 3.20 | 60.96 | Sulfanilamide | − | −0.42 | 48.57 |
| Rifamide | + | 8.94 | 80.65 | Sulfanilic acid | − | −1.20 | 45.90 |
| Rifamycin sv | + | 3.91 | 63.42 | N4-sulfanilylsulfanilamide | + | 2.94 | 60.08 |
| Rifapentine | + | 7.42 | 75.44 | Sulfanilylurea | + | 1.69 | 55.80 |
| Rosaranicin | + | 2.48 | 58.51 | Sulfanitran | + | 2.58 | 58.84 |
| Rosoxacin | − | −1.56 | 44.65 | Sulfaperine | + | 0.90 | 53.07 |
| Rufloxacin | + | 2.04 | 56.99 | Sulfaphenazole | − | −1.40 | 45.20 |
| Salazosulfadimidine | − | −0.44 | 48.50 | Sulfapyrazine | U | 0.48 | 51.64 |
| Sancycline | + | 1.94 | 56.65 | Sulfapyridine | − | −0.53 | 48.18 |
| Sisomicin | + | 8.07 | 77.67 | Sulfasymazine | + | 1.60 | 55.50 |
| Solasulfone | + | 0.83 | 52.86 | Sulfathiazole | − | −0.02 | 49.94 |
| Spectinomycin | + | 0.62 | 52.13 | Sulfathiourea | + | 1.69 | 55.80 |
| Spiramycin | + | 4.99 | 67.11 | Sulfisoxazole | + | 1.26 | 54.32 |
| Streptomycin | + | 14.58 | 100.00 | Sultamicillin | + | 6.42 | 72.00 |
| Succinylsulfathiazole | + | 1.15 | 53.96 | Talampicillin | + | 1.40 | 54.81 |
| Succisulfone | + | 0.59 | 52.03 | Taurolidine | + | 1.31 | 54.50 |
| Sulfacetamide | + | 0.94 | 53.23 | Temafloxacin | + | 3.43 | 61.78 |
| Sulfachlorpyridazine | + | 0.83 | 52.84 | Tetracycline | + | 3.12 | 60.70 |
| Sulfachrysoidine | − | −0.67 | 47.71 | Thiazolsulfone | + | 0.65 | 52.23 |
| Sulfadiazine | U | 0.22 | 50.75 | Tigemonam | + | 2.51 | 58.62 |
| Sulfadicramide | + | 0.59 | 52.04 | Tosufloxacin | + | 3.04 | 60.42 |
| Sulfadoxine | + | 0.52 | 51.78 | Trimethoprim | + | 3.82 | 63.09 |
| Sulfaethidole | + | 0.82 | 52.81 | Xibornol | − | −1.48 | 44.92 |
| Sulfaguanidine | + | 2.44 | 58.37 | | | | |
| (b) Inactive group[b] | | | | | | | |
| Alfentanil | + | 2.15 | 57.38 | 2-Amino-4-picoline | − | −1.42 | 45.12 |
| Allylprodine | − | −4.11 | 35.91 | Aminopropylon | − | −0.18 | 49.39 |
| Alphaprodine | − | −3.42 | 38.27 | Amtolmetin guacil | − | −3.43 | 38.22 |
| Benzylmorphine | − | −4.84 | 33.40 | Antipyrine | − | −1.27 | 45.64 |
| Bezitramide | − | −3.01 | 39.67 | Antrafenine | + | 3.95 | 63.53 |
| Butorphanol | − | −5.73 | 30.37 | Aspirin | − | −2.49 | 41.47 |
| Codeine | − | −3.28 | 38.74 | Benorylate | − | −1.31 | 45.52 |
| Desomorphine | − | −4.51 | 34.54 | Benoxaprofen | − | −3.41 | 38.29 |
| Dextromoramide | − | −8.03 | 22.46 | Benzydamine | − | −3.14 | 39.23 |
| Diampromide | − | −3.33 | 38.60 | Bermoprofen | − | −2.51 | 41.39 |
| Dihydrocodeine | − | −3.28 | 38.74 | bromfenac | − | −2.10 | 42.80 |
| Dihydrocodeinone enol acetate | − | −1.92 | 43.41 | 5-Bromosalicylic acid acetate | − | −1.81 | 43.80 |
| Dimenoxadol | − | −1.59 | 44.55 | Bucetin | − | −2.99 | 39.75 |
| Dimepheptanol | − | −3.61 | 37.63 | Bufexamac | − | −2.78 | 40.46 |
| Dimethylthiambutene | − | −2.91 | 40.00 | Butacetin | − | −2.29 | 42.14 |
| Dipipanone | − | −5.49 | 31.17 | Carbamazepine | − | −3.49 | 38.03 |
| Eptazocine | − | −3.49 | 38.02 | Carbiphene | − | −3.95 | 36.46 |
| Ethoheptazine | − | −4.27 | 35.34 | Chlorthenoxazin(e) | − | −4.23 | 35.48 |
| Ethylmorphine | − | −3.46 | 38.14 | Cinchophen | − | −4.44 | 34.76 |
| Etonitazene | − | −0.60 | 47.93 | Ciramadol | − | −3.25 | 38.86 |
| Fentanyl | − | −3.87 | 36.71 | Clonixin | − | −3.80 | 36.97 |
| Hydromorphone | − | −3.83 | 36.86 | Cropropamide | − | −0.51 | 48.24 |
| Hydroxypethidine | − | −3.84 | 36.85 | Crotethamide | − | −0.34 | 48.84 |
| Isomethadone | − | −3.61 | 37.63 | Diflunisal | − | −0.39 | 48.67 |
| Levorphanol | − | −4.68 | 33.94 | Dioxadrol | − | −6.22 | 28.67 |
| Lofentanil | − | −3.04 | 39.57 | Dipyrocetyl | − | −1.48 | 44.92 |
| Meperidine | − | −4.10 | 35.95 | Enfenamic acid | − | −4.96 | 33.00 |
| Metazocine | − | −2.64 | 40.95 | Epirizole | − | −1.75 | 43.99 |
| Methadone hydrochloride | − | −3.61 | 37.63 | Etersalate | − | −2.14 | 42.65 |
| Metopon | − | −3.33 | 38.59 | Ethoxazene | − | −1.47 | 44.98 |
| Myrophine | − | −5.59 | 30.83 | Etodolac | − | −3.60 | 37.65 |
| Nalbuphine | − | −4.87 | 33.30 | Felbinac | − | −4.37 | 35.01 |
| Narceine | − | −1.56 | 44.65 | Floctafenine | − | −0.40 | 48.64 |
| Normethadone | − | −4.28 | 35.31 | Flufenamic acid | − | −1.15 | 46.05 |

Table 4 (*Continued*)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| Normorphine | – | −4.51 | 34.54 | Fluoresone | – | −2.19 | 42.48 |
| Norpipanone | – | −6.17 | 28.84 | Fluproquazone | – | −2.04 | 43.00 |
| Oxymorphone | – | −3.33 | 38.59 | Flurbiprofen | – | −1.83 | 43.71 |
| Pentazocine | – | −3.16 | 39.16 | Gentisic acid | – | −2.14 | 42.68 |
| Phenadoxone | – | −5.49 | 31.17 | Ibufenac | – | −2.66 | 40.87 |
| Phenoperidine | – | −6.42 | 27.99 | Indomethacin | – | −2.41 | 41.74 |
| Piminodine | – | −4.82 | 33.48 | Isofezolac | – | −7.42 | 24.55 |
| Piritramide | – | −4.52 | 34.50 | Isonixin | – | −3.07 | 39.46 |
| Propiram | – | −3.42 | 38.26 | Ketoprofen | – | −3.19 | 39.06 |
| Propoxyphene | – | −4.06 | 36.06 | Ketorolac | – | −3.59 | 37.69 |
| Remifentanil | – | −2.01 | 43.10 | Lefetamine | – | −2.14 | 42.67 |
| Tilidine | – | −3.78 | 37.05 | Lornoxicam | – | −2.73 | 40.65 |
| Aceclofenac | – | −3.53 | 37.90 | Loxoprofen | – | −3.01 | 39.66 |
| Acetaminophen | – | −1.87 | 43.57 | Metofoline | – | −3.71 | 37.27 |
| Acetanilide | – | −2.55 | 41.25 | Mofezolac | – | −4.24 | 35.47 |
| Acetylsalicylsalicylic acid | – | −2.86 | 40.18 | Morazone | – | −2.30 | 42.12 |
| Alclofenac | – | −3.82 | 36.90 | Naproxen | – | −2.84 | 40.26 |
| Aminochlorthenoxazin | – | −2.47 | 41.53 | Nefopam | – | −5.07 | 32.62 |
| Nifenazone | – | −2.29 | 42.16 | Levophacetoperane | – | −4.11 | 35.92 |
| Parsalmide | – | −2.28 | 42.17 | Maprotiline | – | −5.09 | 32.54 |
| Perisoxal | – | −4.16 | 35.74 | Melitracen | – | −1.61 | 44.48 |
| Phenacetin | – | −2.64 | 40.94 | Metapramine | – | −4.17 | 35.71 |
| Phenocoll | – | −1.39 | 45.22 | Metralindole | – | −2.26 | 42.26 |
| Phenopyrazone | – | −4.00 | 36.27 | Milnacipran | – | −3.22 | 38.96 |
| Phenyl salicylate | – | −4.37 | 35.01 | Minaprine | – | −3.12 | 39.30 |
| Pipebuzone | – | −4.20 | 35.59 | Mirtazepine | – | −5.00 | 32.87 |
| Piperylone | – | −1.72 | 44.10 | Nefazodone | – | −0.79 | 47.30 |
| Propacetamol | – | −0.26 | 49.13 | Nomifensine | – | −4.27 | 35.35 |
| Ramifenazone | – | −0.58 | 48.01 | Nortriptyline | – | −5.51 | 31.11 |
| Salacetamide | – | −2.05 | 42.98 | Octamoxin | – | −1.04 | 46.43 |
| Salicylamide | – | −2.37 | 41.86 | Opipramol | – | −3.83 | 36.87 |
| Salicylsulfuric acid | – | −1.98 | 43.19 | Oxaflozane | – | −1.21 | 45.85 |
| Salsalate | – | −3.19 | 39.06 | Oxypertine | – | −1.11 | 46.21 |
| Salverine | – | −3.02 | 39.64 | Piberaline | – | −4.00 | 36.28 |
| Suprofen | – | −3.01 | 39.66 | Pizotyline | – | −6.06 | 29.23 |
| Talniflumate | – | −1.50 | 44.85 | Protriptyline | – | −5.51 | 31.11 |
| Tenoxicam | – | −2.33 | 42.00 | Pyrisuccideanol | + | 1.38 | 54.72 |
| Tetrandrine | – | −0.80 | 47.27 | Quinupramine | – | −6.21 | 28.72 |
| Tinoridine | – | −5.32 | 31.74 | Ritanserin | – | −3.45 | 38.18 |
| Tolfenamic acid | – | −3.90 | 36.61 | Rolipram | – | −2.60 | 41.07 |
| Tropesin | – | −2.10 | 42.78 | Sertraline | – | −3.79 | 36.99 |
| Viminol | – | −1.80 | 43.83 | Sulpiride | – | −0.22 | 49.24 |
| Xenbucin | – | −3.87 | 36.73 | Tandospirone | – | −2.02 | 43.06 |
| Adinazolam | – | −5.44 | 31.34 | Thiazesim | – | −3.31 | 38.63 |
| Adrafinil | – | −3.66 | 37.46 | Thozalinone | – | −2.20 | 42.45 |
| Amitriptyline | – | −4.83 | 33.44 | Tianeptine | – | −3.18 | 39.08 |
| Amoxapine | – | −4.77 | 33.65 | Toloxatone | – | −2.90 | 40.05 |
| Benactyzine | – | −0.65 | 47.78 | Tranylcypromine | – | −3.39 | 38.36 |
| Benmoxine | – | −4.52 | 34.51 | Venlafaxine | – | −3.47 | 38.11 |
| Binedaline | – | −3.07 | 39.49 | Viloxazine | – | −4.09 | 35.99 |
| Butacetin | – | −2.29 | 42.14 | Acetohexamide | – | −3.36 | 38.49 |
| Butriptyline | – | −4.15 | 35.77 | 1-Butyl-3-metanilylurea | – | −2.30 | 42.10 |
| Caroxazone | – | −1.89 | 43.51 | Carbutamide | U | 0.31 | 51.07 |
| Clomipramine | – | −3.98 | 36.36 | Chlorpropamide | – | −1.65 | 44.34 |
| Cotinine | – | −2.29 | 42.15 | Glibornuride | – | −1.50 | 44.85 |
| Desipramine | – | −5.07 | 32.62 | Gliclazide | – | −3.11 | 39.33 |
| Dibenzepin | – | −4.83 | 33.44 | Glimepiride | U | 0.36 | 51.25 |
| Dimethazan | – | −1.63 | 44.42 | Glipizide | + | 1.95 | 56.70 |
| Dioxadrol | – | −6.22 | 28.67 | Gliquidone | U | 0.10 | 50.33 |
| Dothiepin | – | −4.83 | 33.44 | Glisoxepid | + | 0.81 | 52.79 |
| Doxepin | – | −4.83 | 33.44 | Glibenclamide | – | −2.08 | 42.88 |
| Duloxetine | – | −4.05 | 36.11 | Glybuthiazol(e) | + | 1.32 | 54.54 |

Table 4 (*Continued*)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| Febarbamate | − | −1.99 | 43.18 | Glybuzole | − | −2.23 | 42.36 |
| Femoxetine | − | −5.00 | 32.87 | Glyhexamide | − | −3.57 | 37.74 |
| Fencamine | + | 3.58 | 62.27 | Glymidine | − | −5.28 | 31.89 |
| Fluacizine | U | 0.03 | 50.12 | Glypinamide | − | −2.86 | 40.19 |
| Fluoxetine | − | −1.87 | 43.60 | Karanjin | − | −4.72 | 33.80 |
| Fluvoxamine | − | −1.14 | 46.10 | Phenbutamide | − | −3.24 | 38.89 |
| Imipramine *n*-oxide | − | −3.89 | 36.67 | Tolazamide | − | −2.53 | 41.31 |
| Indalpine | − | −2.78 | 40.48 | Tolbutamide | − | −1.84 | 43.70 |
| Indeloxazine hydrochloride | − | −3.86 | 36.75 | Tolcyclamide | − | −3.03 | 39.62 |
| Iprindole | − | −3.17 | 39.13 | Alacepril | − | −0.74 | 47.46 |
| Iproniazid | U | 0.36 | 51.24 | Alfuzosin | + | 1.01 | 53.48 |
| Isocarboxazid | − | −2.61 | 41.05 | Alprenolol | − | −2.05 | 42.97 |
| Amlodipine | − | −0.69 | 47.63 | Metipranolol | + | 1.39 | 54.76 |
| Amosulalol | − | −4.19 | 35.62 | Metoprolol | − | −2.53 | 41.31 |
| Arotinolol | + | 1.52 | 55.20 | Moprolol | − | −1.87 | 43.57 |
| Barnidipine | − | −1.65 | 44.35 | Moveltipril | U | 0.03 | 50.11 |
| Benazepril | − | −2.63 | 41.00 | Moxonidine | − | −1.77 | 43.95 |
| Benidipine | − | −1.10 | 46.23 | Naftopidil | − | −4.33 | 35.14 |
| Betaxolol | − | −3.56 | 37.78 | Nebivalol | − | −3.18 | 39.11 |
| Bethanidine | − | −2.02 | 43.08 | Nicardipine | U | 0.17 | 50.58 |
| Bevantolol | − | −3.30 | 38.70 | Nifedipine | − | −2.70 | 40.74 |
| Bisoprolol | − | −2.38 | 41.83 | Nipradilol | − | −0.33 | 48.88 |
| Budralazine | − | −2.92 | 39.99 | Nisoldipine | − | −2.48 | 41.49 |
| Bufuralol | − | −2.26 | 42.26 | Nitrendipine | − | −1.31 | 45.52 |
| Bunitrolol | − | −1.04 | 46.44 | Pargyline | − | −3.24 | 38.88 |
| Bupranolol | − | −1.17 | 45.99 | Penbutolol | − | −1.68 | 44.25 |
| Cadralazine | + | 2.51 | 58.61 | Perindopril | − | −1.50 | 44.86 |
| Candesartan | − | −1.43 | 45.09 | Phentolamine | − | −4.62 | 34.14 |
| Captopril | − | −0.69 | 47.62 | Pinacidil | − | −0.16 | 49.45 |
| Carazolol | − | −1.12 | 46.15 | Pindolol | − | −1.16 | 46.03 |
| Carmoxirole | − | −3.40 | 38.33 | Piperoxan | − | −5.54 | 30.99 |
| Carteolol | − | −0.15 | 49.48 | Prazosin | − | −3.58 | 37.71 |
| Carvedilol | − | −4.20 | 35.59 | Pronethalol | − | −3.02 | 39.64 |
| Cetamolol | − | −0.21 | 49.28 | Ramipril | − | −0.92 | 46.84 |
| Ciclosidomine | − | −2.82 | 40.34 | Raubasine | − | −5.71 | 30.43 |
| Clonidine | − | −3.31 | 38.65 | Rescimetol | − | −3.69 | 37.33 |
| Delapril | − | −1.51 | 44.83 | Reserpine | − | −2.29 | 42.14 |
| Deserpidine | − | −2.76 | 40.52 | Rilmenidine | − | −2.97 | 39.82 |
| Dihydralazine | − | −2.21 | 42.43 | Spirapril | − | −2.78 | 40.47 |
| Doxazosin | − | −3.08 | 39.44 | Sulfinalol | − | −3.21 | 38.99 |
| Enalapril | − | −0.74 | 47.45 | Talinolol | − | −0.51 | 48.24 |
| Epanolol | − | −2.33 | 41.99 | Temocapril | − | −3.97 | 36.38 |
| Eprosartan | − | −4.45 | 34.74 | Tertatolol | − | −1.50 | 44.85 |
| Fantofarone | − | −3.32 | 38.63 | Timolol | + | 1.97 | 56.75 |
| Felodipine | − | −3.53 | 37.90 | Todralazine | − | −3.57 | 37.76 |
| Fenoldopam | − | −4.81 | 33.50 | Toliprolol | − | −1.28 | 45.60 |
| Guanabenz | − | −3.39 | 38.38 | Tolonidine | − | −3.16 | 39.16 |
| Guanacline | − | −0.18 | 49.37 | Trimazosin | + | 0.64 | 52.21 |
| Guanadrel | − | −0.54 | 48.13 | Urapidil | + | 1.28 | 54.40 |
| Guanethidine | U | 0.23 | 50.80 | Valsartan | + | 1.20 | 54.13 |
| Guanfacine | − | −3.49 | 38.03 | Acrivastine | − | −5.09 | 32.55 |
| Guanochlor | U | 0.20 | 50.68 | Ahistan | − | −3.82 | 36.90 |
| Guanoxan | − | −0.37 | 48.74 | Alloclamide | − | −3.03 | 39.62 |
| Hydracarbazine | U | 0.33 | 51.13 | Astemizole | − | −2.28 | 42.20 |
| Hydralazine | − | −2.42 | 41.69 | Azatadine | − | −6.16 | 28.88 |
| Imidapril | + | 2.06 | 57.05 | Azelastine | − | −3.95 | 36.46 |
| Indoramin | − | −3.50 | 38.01 | Bromodiphenhydramine | − | −3.32 | 38.62 |
| Irbesartan | − | −1.27 | 45.63 | Brompheniramine | − | −3.35 | 38.51 |
| Isradipine | − | −2.79 | 40.43 | Carbinoxamine | − | −4.45 | 34.73 |
| Ketanserin | − | −2.26 | 42.26 | Cetirizine | − | −4.79 | 33.57 |
| Labetalol | − | −3.69 | 37.35 | Cetoxime | − | −4.29 | 35.30 |
| Lacidipine | − | −1.04 | 46.42 | Chlorothen | − | −3.99 | 36.32 |

Table 4 (*Continued*)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| Levcromakalim | − | −0.01 | 49.96 | Chlorpheniramine | − | −3.68 | 37.39 |
| Lisinopril | + | 0.61 | 52.08 | Cinnarizine | − | −6.54 | 27.57 |
| Manidipine | − | −0.82 | 47.19 | Clobenztropine | − | −3.05 | 39.53 |
| Mecamylamine | − | −1.20 | 45.90 | Clocinizine | − | −6.19 | 28.77 |
| Methyldopa | − | −0.94 | 46.76 | Cyproheptadine | − | −5.51 | 31.11 |
| Methyl 4-pyridyl ketone thiosemicarbazone | + | 1.37 | 54.70 | Deptropine | − | −1.96 | 43.29 |
| Dimethindene | − | −2.26 | 42.24 | Oxaprozin | − | −5.31 | 31.79 |
| Diphenhydramine | − | −4.00 | 36.29 | Phenylbutazone | − | −4.19 | 35.63 |
| Diphenylpyraline | − | −3.40 | 38.33 | Piroxicam | − | −2.93 | 39.97 |
| Ebastine | − | −3.57 | 37.75 | Pirprofen | − | −3.86 | 36.76 |
| Embramine | − | −2.82 | 40.34 | Proglumetacin | + | 2.19 | 57.51 |
| Emedastine | − | −3.56 | 37.80 | Protizinic acid | − | −2.07 | 42.90 |
| Etymemazine | − | −2.23 | 42.35 | Sulindac | − | −1.59 | 44.53 |
| Fexofenadine | − | −3.84 | 36.84 | Suxibuzone | − | −3.44 | 38.19 |
| Histapyrrodine | − | −6.59 | 27.41 | Tiaprofenic acid | − | −3.01 | 39.66 |
| Hydroxyethylpromethazine-n | − | −4.01 | 36.26 | Tolmetin | − | −2.65 | 40.92 |
| Hydroxyzine | − | −5.47 | 31.25 | Zaltoprofen | − | −3.19 | 39.06 |
| Isopromethazine | − | −3.82 | 36.90 | Acefylline | + | 0.63 | 52.17 |
| Levocabastine | − | −3.58 | 37.73 | Acetazolamide | U | 0.14 | 50.46 |
| Loratadine | − | −5.29 | 31.87 | Althiazide | − | −2.19 | 42.50 |
| Mebhydroline | − | −4.24 | 35.45 | Amanozine | − | −1.54 | 44.73 |
| Medrylamine | − | −3.50 | 38.01 | Amiloride | + | 3.81 | 63.05 |
| Methaphenilene | − | −5.43 | 31.39 | Amisometradine | + | 1.04 | 53.58 |
| Methapyrilene | − | −4.65 | 34.06 | Azosemide | − | −3.60 | 37.66 |
| Moxastine | − | −3.50 | 38.01 | Bendroflumethiazide | U | 0.33 | 51.15 |
| Orphenadrine | − | −3.74 | 37.19 | Benzylhydrochlorothiazide | − | −3.72 | 37.26 |
| Pheniramine | − | −4.34 | 35.13 | Bumetanide | − | −2.72 | 40.67 |
| Promethazine | − | −3.82 | 36.90 | Buthiazide | − | −1.83 | 43.72 |
| Pyrrobutamine | − | −6.00 | 29.42 | Chloraminophenanide | − | −0.94 | 46.79 |
| Setastine | − | −5.20 | 32.15 | Chlorazanil | − | −2.02 | 43.09 |
| Talastine | − | −3.58 | 37.73 | Chlorothiazide | − | −2.21 | 42.42 |
| Terfenadine | − | −4.34 | 35.11 | Clofenamide | − | −0.72 | 47.54 |
| Thenyldiamine | − | −4.65 | 34.06 | Clopamide | − | −1.61 | 44.48 |
| Tolpropamine | − | −3.37 | 38.43 | Cyclopenthiazide | − | −3.54 | 37.86 |
| Tripelennamine | − | −4.52 | 34.51 | Cyclothiazide | − | −4.04 | 36.15 |
| Triprolidine | − | −5.89 | 29.80 | Disulfamide | − | −0.70 | 47.59 |
| Tritoqualine | − | −2.69 | 40.78 | Ethacrynic acid | − | −3.27 | 38.79 |
| Zolamine | − | −2.78 | 40.48 | Ethiazide | − | −0.98 | 46.63 |
| Acemetacin | − | −1.23 | 45.80 | Ethoxzolanide | − | −1.05 | 46.39 |
| Amfenac | − | −3.50 | 37.99 | Fenquizone | − | −3.71 | 37.29 |
| Ampiroxicam | − | −1.00 | 46.56 | Furosemide | − | −3.47 | 38.11 |
| Bromosaligenin | − | −2.81 | 40.35 | Hydracarbazine | U | 0.33 | 51.13 |
| Bucloxic acid | − | −4.67 | 33.97 | Hydrochlorothiazide | − | −2.21 | 42.42 |
| Clidanac | − | −5.00 | 32.85 | Indapamide | − | −3.14 | 39.23 |
| Clopirac | − | −1.71 | 44.14 | Isosorbide | − | −3.32 | 38.62 |
| Diclofenac | − | −4.71 | 33.84 | Methazolamide | + | 0.81 | 52.79 |
| Etofenamate | − | −1.90 | 43.49 | Methyclothiazide | − | −1.70 | 44.16 |
| Fenbufen | − | −4.04 | 36.13 | Metochalcone | − | −3.72 | 37.25 |
| Fenclozic acid | − | −3.74 | 37.17 | Metolazone | − | −0.98 | 46.64 |
| Fendosal | − | −5.32 | 31.75 | Morpholinomethyltheophylline | − | −2.53 | 41.31 |
| Fentiazac | − | −4.78 | 33.60 | Muzolimine | − | −0.43 | 48.53 |
| Feprazone | − | −3.51 | 37.96 | Paraflutizide | − | −3.57 | 37.74 |
| Flunoxaprofen | − | −2.79 | 40.42 | Perhexiline | − | −6.49 | 27.76 |
| Ibuprofen | − | −1.98 | 43.19 | Piretanide | − | −4.03 | 36.19 |
| Indoprofen | − | −3.58 | 37.72 | Polythiazide | U | 0.14 | 50.49 |
| Isoxicam | − | −2.07 | 42.90 | Teclothiazide | − | −1.76 | 43.95 |
| Lonazolac | − | −5.10 | 32.53 | Theobromine | U | 0.30 | 51.04 |
| Meclofenamic acid | − | −4.53 | 34.46 | Torsernide | + | 1.11 | 53.82 |
| Metiazinic acid | − | −3.25 | 38.85 | Triamterene | − | −0.91 | 46.87 |
| Mofebutazone | − | −2.47 | 41.51 | Xipamide | − | −0.71 | 47.56 |
| Niflumic acid | − | −2.30 | 42.13 | Acifran | − | −2.84 | 40.26 |

Table 4 (*Continued*)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| Oxametacine | – | −1.30 | 45.55 | Acipimox | – | −0.24 | 49.17 |
| Atorvastatin | – | −2.69 | 40.77 | Clomethiazole | – | −3.03 | 39.61 |
| Azacosterol | – | −1.17 | 45.99 | Cyclopentobarbital | – | −2.81 | 40.37 |
| Beclobrate | – | −3.72 | 37.25 | Doxylamine | – | −3.89 | 36.67 |
| Benzalbutyramide | – | −2.67 | 40.84 | Ectylurea | – | −0.08 | 49.74 |
| Binifibrate | – | −1.66 | 44.32 | Enallylpropymal | – | −0.42 | 48.55 |
| Ciprofibrate | – | −2.97 | 39.83 | Estazolam | – | −5.71 | 30.43 |
| Clofibrate | – | −2.66 | 40.87 | Etaqualone | – | −3.66 | 37.44 |
| Clofibric acid | – | −2.31 | 42.07 | Ethinamate | – | −2.90 | 40.05 |
| Clomestrone | – | −4.17 | 35.69 | Etodroxizine | – | −5.69 | 30.50 |
| Eritadenine | U | 0.29 | 50.99 | Fenadiazole | – | −3.30 | 38.67 |
| Etofibrate | – | −2.81 | 40.37 | Flunitrazepam | – | −2.17 | 42.55 |
| Fenofibrate | – | −2.18 | 42.51 | Furfuryl-5-isopropylbarbituric | – | −2.13 | 42.69 |
| Furazabol | – | −0.37 | 48.74 | Glutethimide | – | −3.25 | 38.85 |
| Lovastatin | – | −2.03 | 43.03 | Haloxazolam | – | −3.59 | 37.70 |
| Melinamide | – | −5.23 | 32.07 | Hexethal | – | −1.01 | 46.52 |
| Mytatrienediol | – | −2.69 | 40.78 | Hexobarbital | – | −1.28 | 45.61 |
| Nicoclonate | – | −3.13 | 39.27 | Homofenazine | U | 0.01 | 50.05 |
| Nicofibrate | – | −3.45 | 38.16 | Loprazolam | – | −3.47 | 38.09 |
| Oryzanol | – | −1.93 | 43.37 | Mecloxamine | – | −2.47 | 41.55 |
| Oxiniacic acid | – | −2.04 | 43.02 | Meparfynol | – | −1.96 | 43.28 |
| Phenylbutyramide | – | −2.73 | 40.65 | Mephobarbital | – | −2.13 | 42.69 |
| Pirifibrate | – | −1.39 | 45.22 | Methaqualone | – | −3.15 | 39.20 |
| Pirozadil | + | 0.70 | 52.39 | Methyl-4-thiazoleethanol-5 | – | −2.38 | 41.85 |
| Probucol | + | 3.37 | 61.56 | Narcobarbital | U | 0.26 | 50.88 |
| Ronifibrate | – | −2.98 | 39.77 | Nealbarbital | – | −0.10 | 49.66 |
| Simvastatin | – | −1.53 | 44.75 | Niaprazine | – | −0.76 | 47.40 |
| Sultosilic acid | – | −1.51 | 44.83 | Nitrazepam | – | −3.32 | 38.60 |
| Theofibrate | + | 4.18 | 64.33 | Novonal | – | −1.37 | 45.31 |
| Triparanol | – | −3.17 | 39.12 | Paraldehyde | – | −2.64 | 40.95 |
| Acecarbromal | U | 0.08 | 50.27 | Pentobarbital | – | −1.28 | 45.62 |
| Allobarbital | – | −1.28 | 45.61 | Phenobarbital | – | −2.81 | 40.37 |
| Amobarbital | – | −0.60 | 47.94 | Phenylmethylbarbituric acid | – | −1.96 | 43.29 |
| Amphenidone | – | −2.88 | 40.13 | Piperidione | – | −2.05 | 42.98 |
| Apronalide | – | −0.33 | 48.88 | Propiomazine | – | −2.12 | 42.73 |
| Barbital | – | −0.93 | 46.82 | Proxibarbal | – | −0.60 | 47.94 |
| Brallobarbital | – | −0.60 | 47.94 | Pyrithyldione | – | −2.05 | 42.98 |
| Brotizolam | – | −3.70 | 37.32 | Rilmazafone | U | 0.16 | 50.55 |
| Butabarbital | – | −1.10 | 46.23 | Secobarbital | – | −1.45 | 45.02 |
| Butallylonal | – | −0.60 | 47.95 | Sulfonmethane | U | 0.05 | 50.18 |
| Butethal | – | −1.28 | 45.61 | Temazepam | – | −3.72 | 37.25 |
| Butoctamide | – | −2.23 | 42.34 | Tetrabarbital | – | −1.45 | 45.02 |
| Carbubarb | – | −2.31 | 42.09 | Triazolam | – | −5.36 | 31.62 |
| Carfimate | – | −2.98 | 39.78 | Vinbarbital | – | −1.28 | 45.62 |
| Chlorhexadol | – | −0.93 | 46.81 | Zolpidem | – | −3.06 | 39.51 |
| Cinolazepam | – | −3.29 | 38.73 | | | | |

[a] PA: probability of activity (%), undetermined (U) = 5.33%, false inactivity (−) = 20.71%, overall accuracy = 73.96%, adjusted accuracy = 78.13%.
[b] PA: probability of activity (%), undetermined (U) = 3.97%, false activity (+) = 5.10%, overall accuracy = 90.93%, adjusted accuracy = 94.69%.

Overall accuracy was 73.96% in the active group and 90.93% in the inactive group. These percentages increase to 78.13 and 94.69%, respectively, if the undetermined molecules are eliminated. The cross-validation test was applied to the $\Delta P$ function with a group of 72 antibacterials and 202 theoretical inactives not used in the discriminant function. Table 6 shows the results obtained (only the first 10 actives and inactives, the complete results are available as supplementary information). The fact that both the overall accuracy (70.83% for active group, 92.57% for inactive group) and the adjusted accuracy (79.69% for active group, 93.97% for inactive group) are similar to those of the group used in the LDA demonstrates the quality of the selected discriminant function.

The equation obtained should, if possible, identify a high percentage of the non-antibacterials (about 94%), even though the percentage of correct identifications in the active group may decrease (about 79%). In this context it should be pointed out that in both the discriminant analysis itself and the validation test, the percentage of false positives is very small (5.10% and 5.94%, respectively), which is what we need to design and select molecules correctly.

Table 5
Supplementary information: results obtained by applying the final discriminant function to a group of 72 active compounds and a group of 202 inactive compounds not included in the LDA (cross-validation)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| (a) Active group[a] | | | | | | | |
| Acetyl sulfamethoxypyrazine | + | 1.51 | 55.16 | Micronomicin | + | 7.48 | 75.64 |
| Amdinocillin | U | 0.13 | 50.43 | Nalidixic acid | − | −1.78 | 43.90 |
| Amoxicillin | + | 2.55 | 58.74 | Nifuratel | − | −0.68 | 47.65 |
| Apicycline | + | 8.72 | 79.91 | Nifurtoinol | + | 0.84 | 52.88 |
| Arbekacin | + | 9.64 | 83.07 | Oleandomycin | + | 3.44 | 61.80 |
| Azidocillin | + | 3.91 | 63.41 | Oxolinic acid | − | −3.07 | 39.46 |
| Azithromycin | + | 5.96 | 70.43 | Penamecillin | − | −1.06 | 46.37 |
| Benzylpenicillinic acid | − | −0.17 | 49.40 | Penicillin o | + | 0.71 | 52.43 |
| Carumonam | + | 5.04 | 67.30 | Phthatylsulfathiazole | U | 0.13 | 50.44 |
| Cefamandole | + | 5.00 | 67.16 | Pipemidic acid | − | −0.22 | 49.25 |
| Cefazolin | + | 9.60 | 82.92 | Pivampicillin | + | 4.58 | 65.70 |
| Cefditoren | + | 4.34 | 64.88 | Ribostamycin | + | 6.53 | 72.41 |
| Cefmenoxime | + | 8.91 | 80.55 | Rifampin | + | 9.45 | 82.42 |
| Cefoperazone | + | 11.86 | 90.69 | Rokitamycin | + | 3.08 | 60.57 |
| Cefotiam | + | 9.30 | 81.90 | Rolitetracycline | + | 4.65 | 65.96 |
| Cefprozil | + | 0.77 | 52.62 | Roxithromycin | + | 5.21 | 67.87 |
| Ceftezole | + | 8.20 | 78.11 | Sparfloxacin | + | 3.10 | 60.64 |
| Ceftriaxone | + | 8.43 | 78.92 | Sulbenicillin | − | −0.75 | 47.43 |
| Cephacetrile sodium | + | 0.76 | 52.61 | Sulfabenzamide | − | −1.12 | 46.18 |
| Cephalosporin c | + | 2.65 | 59.09 | Sulfacytine | + | 1.71 | 55.85 |
| Cinoxacin | − | −2.30 | 42.13 | Sulfadimethoxine | + | 1.19 | 54.09 |
| Clometocillin | − | −0.46 | 48.41 | Sulfaguanole | + | 1.78 | 56.12 |
| Diathymosulfone | + | 0.64 | 52.20 | Sulfamerazine | U | 0.22 | 50.76 |
| Dicloxacillin | − | −3.40 | 38.34 | Sulfamethomidine | + | 1.37 | 54.70 |
| Doxycycline | + | 2.54 | 58.72 | Sulfametrole | + | 0.82 | 52.81 |
| Enoxacin | + | 1.87 | 56.43 | 4-Sulfanilamidosalicylic acid | U | 0.24 | 50.83 |
| *n*-2-Formylsulfisomidine | + | 1.50 | 55.15 | *p*-Sulfanilylbenzylamine | − | −0.48 | 48.36 |
| Fortimicin a | + | 6.38 | 71.87 | *n*-Sulfanilyl-3,4-xylamide | U | 0.24 | 50.83 |
| Grepafloxacin | + | 1.28 | 54.39 | Sulfaproxyline | + | 0.92 | 53.16 |
| Hetacillin | + | 0.97 | 53.34 | Sulfasomizole | + | 0.58 | 52.00 |
| Josamycin | + | 3.04 | 60.41 | Sulfisomidine | + | 1.55 | 55.30 |
| Lincomycin | U | 0.39 | 51.34 | Tetroxoprim | + | 3.29 | 61.28 |
| Meropenem | + | 4.74 | 66.27 | Thiamphenicol | + | 1.23 | 54.21 |
| Methacycline | + | 2.54 | 58.72 | Ticarcillin | − | −0.32 | 48.89 |
| Methenamine | + | 1.14 | 53.91 | Trospectomycin | U | 0.09 | 50.32 |
| Methicillin sodium | U | 0.22 | 50.77 | Trovafloxacin | + | 2.46 | 58.44 |
| (b) Inactive group[b] | | | | | | | |
| Anileridine | − | −4.10 | 35.95 | Iproclozide | − | −0.91 | 46.88 |
| Clonitazene | − | −2.03 | 43.04 | Lofepramine | − | −5.57 | 30.91 |
| Dezocine | − | −3.59 | 37.69 | Medifoxanine | − | −4.95 | 33.02 |
| Dihydromorphine | − | −3.83 | 36.86 | Mianserin | − | −5.10 | 32.52 |
| Dioxaphetyl butyrate | − | −6.76 | 26.82 | Moclobemide | − | −3.94 | 36.49 |
| Ethylmethylthiambutene | − | −3.09 | 39.40 | Nefopam | − | −5.07 | 32.62 |
| Hydrocodone | − | −3.28 | 38.74 | Nialamide | − | −0.75 | 47.42 |
| Ketobemidone | − | −3.24 | 38.88 | Noxiptilin | − | −2.19 | 42.50 |
| Meptazinol | − | −3.43 | 38.24 | paroxetine | − | −3.93 | 36.52 |
| Morphine | − | −3.83 | 36.86 | Prolintane | − | −4.79 | 33.59 |
| Norlevorphanol | − | −5.36 | 31.61 | Propizepine | − | −3.35 | 38.49 |
| Oxycodone | − | −2.78 | 40.47 | Rolicyprine | − | −2.54 | 41.30 |
| Phenazocine | − | −5.05 | 32.69 | Roxindole | − | −3.91 | 36.60 |
| Proheptazine | − | −3.60 | 37.67 | Tofenacin | − | −4.41 | 34.86 |
| Sufentanil | − | −4.22 | 35.52 | Trazodone | − | −0.89 | 46.94 |
| Acetaminosalol | − | −1.63 | 44.40 | Trimipramine | − | −3.71 | 37.28 |
| Alminoprofen | − | −1.88 | 43.57 | l-Tryptophan | − | −2.20 | 42.45 |
| Aminopyrine | − | −1.08 | 46.30 | Zimeldine | − | −3.12 | 39.30 |
| Apazone | − | −2.83 | 40.29 | Acebutolol | + | 1.66 | 55.68 |
| Benzpiperylon | − | −3.93 | 36.51 | Ajmaline | − | −4.06 | 36.07 |
| *p*-Bromoacetanilide | − | −1.87 | 43.57 | Aranidipine | − | −2.48 | 41.49 |
| Bumadizon | − | −5.29 | 31.85 | Atenolol | − | −0.59 | 47.97 |

Table 5 (*Continued*)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| Carsalam | – | −2.89 | 40.09 | Bopindolol | – | −0.75 | 47.42 |
| Clometacin | – | −2.10 | 42.80 | Bunazosin | – | −4.01 | 36.23 |
| Difenamizole | – | −3.08 | 39.44 | Butofilolol | + | 0.95 | 53.25 |
| Emorfazone | – | −2.45 | 41.60 | Celiprolol | + | 2.58 | 58.84 |
| Ethenzamide | – | −2.73 | 40.65 | Cicletanine | – | −3.10 | 39.38 |
| Fenoprofen | – | −3.87 | 36.73 | Cilazapril | – | −1.47 | 44.96 |
| Flupirtine | – | −0.30 | 48.96 | Cilnidipine | – | −2.95 | 39.88 |
| Glafenine | – | −4.04 | 36.15 | Clentiazem | U | 0.36 | 51.24 |
| Isoladol | – | −3.37 | 38.44 | Debrisoquin | – | −2.34 | 41.97 |
| *p*-Lactophenetide | – | −1.61 | 44.48 | Dilevalol | – | −3.69 | 37.35 |
| Methotrimeprazine | – | −2.23 | 42.35 | Enalaprilat | – | −0.36 | 48.75 |
| Morpholine | – | −3.22 | 38.96 | Endralazine | + | 0.96 | 53.29 |
| 5′-Nitro-2′-propoxyacetanilide | – | −0.81 | 47.23 | Flosequinan | – | −1.45 | 45.02 |
| Phenazopyridine hydrochloride | – | −0.68 | 47.68 | Guanazodine | – | −0.62 | 47.87 |
| Phenyramidol | – | −3.78 | 37.05 | Guanoxabenz | – | −3.90 | 36.62 |
| Propyphenazone | – | −1.44 | 45.06 | Lercanidipine | – | -0.53 | 48.17 |
| Salicylamide *o*-acetic acid | – | −3.05 | 39.53 | Lofexidine | – | −4.08 | 36.01 |
| Simetride | – | −0.71 | 47.56 | Losartan | – | −0.89 | 46.96 |
| Terofenamate | – | −4.93 | 33.10 | Mebutamate | + | 2.49 | 58.53 |
| Tramadol | – | −3.37 | 38.44 | Mepindolol | – | −0.48 | 48.36 |
| Zomepirac | – | −2.30 | 42.12 | Mibefradil | – | −0.26 | 49.11 |
| Amitriptylinoxide | – | −4.33 | 35.16 | Nadolol | – | −0.14 | 49.51 |
| Bupropion | – | −1.36 | 45.34 | Nilvadipine | + | 0.87 | 52.99 |
| Citalopram | – | −0.58 | 48.02 | Oxprenolol | – | −2.23 | 42.37 |
| Demexiptiline | – | −2.87 | 40.17 | Pempidine | – | −0.18 | 49.38 |
| Dimetacrine | – | −1.84 | 43.68 | Pildralazine | + | 2.83 | 59.70 |
| Etoperidone | U | 0.47 | 51.60 | Propranolol | – | −2.00 | 43.13 |
| Fenpentadiol | – | −1.81 | 43.80 | Quinapril | – | −2.05 | 42.95 |
| 5-Hidroxitriptófano (oxitriptan) | – | −1.94 | 43.35 | Rescinnamine | – | −3.37 | 38.46 |
| Imipramine | – | −4.39 | 34.95 | Semotiadil | – | −2.82 | 40.32 |
| Sotalol | + | 0.68 | 52.32 | Etozolin | – | −2.00 | 43.14 |
| Syrosingopine | – | −2.14 | 42.66 | Hydroflumethiazide | + | 1.84 | 56.31 |
| Terazosin | – | −3.58 | 37.71 | Mannitol | – | −0.95 | 46.73 |
| Tiamenidine | – | −1.49 | 44.90 | Mefruside | – | −1.88 | 43.57 |
| Tilisolol | + | 1.33 | 54.56 | Meticrane | – | −1.46 | 45.00 |
| Trandolapril | – | −1.85 | 43.66 | Protheobromine | – | −0.20 | 49.32 |
| Antazoline | – | −6.16 | 28.89 | Quinethazone | – | −1.15 | 46.06 |
| Bamipine | – | −4.03 | 36.20 | Ticrynafen | – | −4.80 | 33.54 |
| Chlorcyclizine | – | −4.56 | 34.36 | Trichlormethiazide | – | −1.61 | 44.47 |
| Chloropyramine | – | −3.44 | 38.20 | Tripamide | – | −4.32 | 35.19 |
| Clemastine | – | −2.73 | 40.65 | Benfluorex | – | −2.71 | 40.71 |
| Clemizole | – | −5.57 | 30.90 | Bezafibrate | – | −2.63 | 40.99 |
| Clobenzepam | – | −4.34 | 35.11 | Clinofibrate | – | −2.59 | 41.13 |
| Doxylamine | – | −3.89 | 36.67 | Eicosapentaenoic acid-(all-z)-5,8,11,14,17 | – | −5.28 | 31.91 |
| Epinastine | – | −4.48 | 34.63 | Fluvastatin | – | −2.33 | 41.99 |
| Fenethazine | – | −4.50 | 34.58 | Gemfibrozil | – | −1.83 | 43.71 |
| Isothipendyl | – | −3.38 | 38.41 | Meglutol | – | −0.95 | 46.73 |
| Mequitazine | – | −6.01 | 29.40 | Niceritrol | U | 0.28 | 50.97 |
| Methafurylene | – | −4.65 | 34.06 | Nicomol | + | 3.15 | 60.81 |
| Methyldiphenhydramine-*p* | – | −3.32 | 38.62 | Pentaerythritol tetraacetate | – | −1.00 | 46.56 |
| Metron s | – | −0.69 | 47.62 | Pravastatin sodium | – | −0.85 | 47.08 |
| Phenindamine | – | −5.20 | 32.16 | Simfibrate | – | −2.89 | 40.10 |
| Phenyltoloxamine | – | −3.17 | 39.14 | Sitosterol-β | – | −2.21 | 42.42 |
| Pyrilamine | – | −3.71 | 37.29 | Xenbucin | – | −3.87 | 36.73 |
| Thenaldine | – | −3.85 | 36.80 | Aprobarbital | – | −1.10 | 46.23 |
| Thonzylamine | – | −2.62 | 41.02 | Butalbital | – | −0.60 | 47.94 |
| Butibufen | – | −2.16 | 42.59 | Capuride | – | −0.33 | 48.88 |
| Cinmetacin | – | −3.19 | 39.06 | Chloralose-α | – | −3.27 | 38.79 |
| Droxicam | – | −3.60 | 37.65 | Cyclobarbital | – | −2.81 | 40.37 |
| Glucametacin | + | 1.03 | 53.52 | Doxefazepam | – | −2.84 | 40.25 |

Table 5 (*Continued*)

| Compound | Classification | $\Delta P$ | PA | Compound | Classification | $\Delta P$ | PA |
|---|---|---|---|---|---|---|---|
| Ibuproxam | – | −1.07 | 46.32 | Ethchlorvynol | – | −3.29 | 38.71 |
| Isoxepac | – | −3.87 | 36.73 | Etomidate | – | −3.74 | 37.17 |
| Mefenamic acid | – | −3.25 | 38.86 | Flurazepam | – | −1.31 | 45.51 |
| Mesalamine | – | −1.36 | 45.34 | Heptabarbital | – | −2.98 | 39.76 |
| Olsalazine | – | −1.80 | 43.82 | Hexapropymate | – | −3.08 | 39.45 |
| Oxyphenbutazone | – | −3.51 | 37.96 | Isovaleryl diethylamide | – | −0.85 | 47.07 |
| Piketoprofen | – | −2.29 | 42.14 | Lormetazepam | – | −4.36 | 35.06 |
| Pirazolac | – | −4.87 | 33.28 | Mecloqualone | – | −4.13 | 35.83 |
| Pranoprofen | – | −1.88 | 43.54 | Methitural | – | −1.63 | 44.42 |
| Tiaramide | – | −1.00 | 46.59 | Methyprylon | – | −1.37 | 45.31 |
| Ximoprofen | – | −2.10 | 42.78 | Perlapine | – | −5.18 | 32.25 |
| Ambuside | – | −0.93 | 46.81 | Phenallymal | – | −2.98 | 39.76 |
| Aminometradine | – | −0.15 | 49.49 | Propallylonal | – | −0.42 | 48.55 |
| Arbutin | – | −2.34 | 41.99 | Quazepam | – | −0.57 | 48.05 |
| Benzthiazide | – | −3.61 | 37.63 | Reposal | – | −2.81 | 40.37 |
| Butazolamide | – | −0.25 | 49.16 | Sulfonethylmethane | – | −0.12 | 49.57 |
| Chlortalidone | – | −1.85 | 43.66 | Talbutal | – | −1.28 | 45.62 |
| Clorexolone | – | −2.23 | 42.34 | Trimetozine | – | −3.00 | 39.70 |
| Epithiazide | – | −0.12 | 49.59 | Vinylbital | – | −1.28 | 45.62 |

[a] PA: probability of activity (%), undetermined (U) = 11.11%, false inactivity (−) = 18.06%, overall accuracy = 70.83%, adjusted accuracy = 79.69%.
[b] PA: probability of activity (%), undetermined (U) = 1.49%, false activity (+) = 5.94%, overall accuracy = 92.57%, adjusted accuracy = 93.97%.

In view of the above, the discrimination of activity carried out shows that the obtained values in the LDA for the antibacterial and non-antibacterial groups make it possible to separate the two populations. Fig. 2 gives the histogram of frequencies (pharmacological distribution diagram [19]) obtained by depicting all the values of the LDA. On it we can observe that the maximun of the $E_i$ (inactivity expectancy) and $E_a$ (activity expectancy) values are distributed on different sides of $\Delta P = 0$. We obtain positive values for active compounds (with a maximum value around $\Delta P = 1$)

Table 6
Results obtained by applying the final discriminant function to a group of 72 active compounds and a group of 202 inactive compounds not included in the LDA (cross-validation), containing data for the first 10 actives and inactives

| Compound | Classiication | $\Delta P$ | PA |
|---|---|---|---|
| (a) Active group[a] | | | |
| Acetyl Sulfamethoxypyrazine | + | 1.51 | 55.16 |
| Amdinocillin | U | 0.13 | 50.43 |
| Amoxicillin | + | 2.55 | 58.74 |
| Apicycline | + | 8.72 | 79.91 |
| Arbekacin | + | 9.64 | 83.07 |
| Azidocillin | + | 3.91 | 63.41 |
| Azithromycin | + | 5.96 | 70.43 |
| Benzylpenicillinic acid | – | −0.17 | 49.40 |
| Carumonam | + | 5.04 | 67.30 |
| Cefamandole | + | 5.00 | 67.16 |
| (b) Inactive group[b] | | | |
| Anileridine | – | −4.10 | 35.95 |
| Clonitazene | – | −2.03 | 43.04 |
| Dezocine | – | −3.59 | 37.69 |
| Dihydromorphine | – | −3.83 | 36.86 |
| Dioxaphetyl butyrate | – | −6.76 | 26.82 |
| Ethylmethylthiambutene | – | −3.09 | 39.40 |
| Hydrocodone | – | −3.28 | 38.74 |
| Ketobemidone | – | −3.24 | 38.88 |
| Meptazinol | – | −3.43 | 38.24 |
| Morphine | – | −3.83 | 36.86 |

The complete results are available as supplementary information.
[a] PA: probability of Activity (%), undetermined (U) = 11.11%, false inactivity (−) = 18.06%, overall accuracy = 70.83%, adjusted accuracy = 79.69%.
[b] PA: probability of activity (%), undetermined (U) = 1.49%, false activity (+) = 5.94%, overall accuracy = 92.57%, adjusted accuracy = 93.97%.

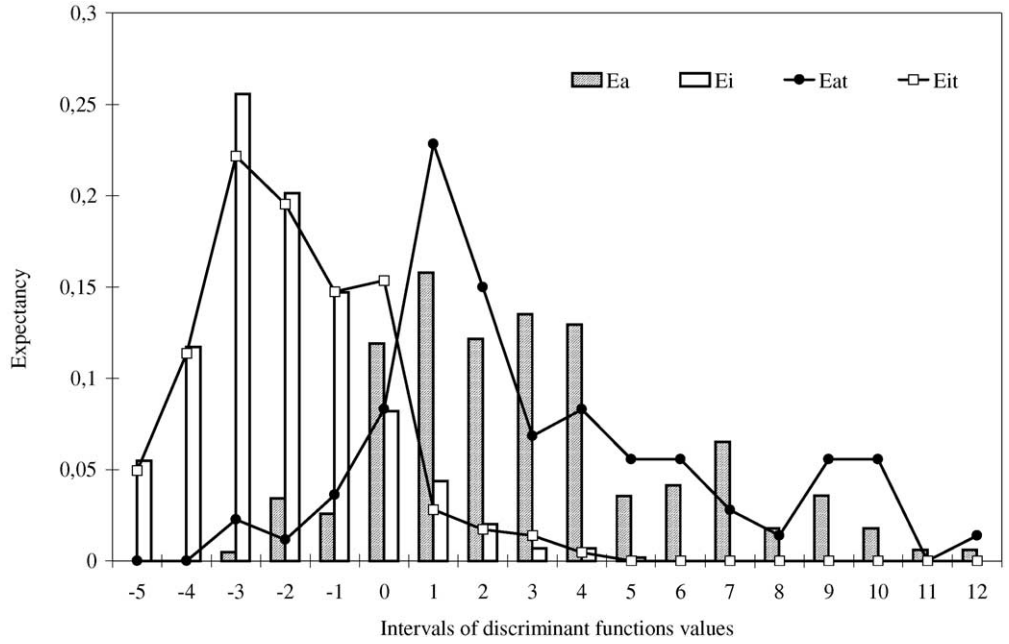


Fig. 2. Pharmacological distribution diagram (PDD) for the discriminant function of antibacterial activity ($E_a$ and $E_{at}$, activity expectancy of reference and test groups, respectively, $E_i$ and $E_{it}$, inactivity expectancy of reference and test groups, respectively).

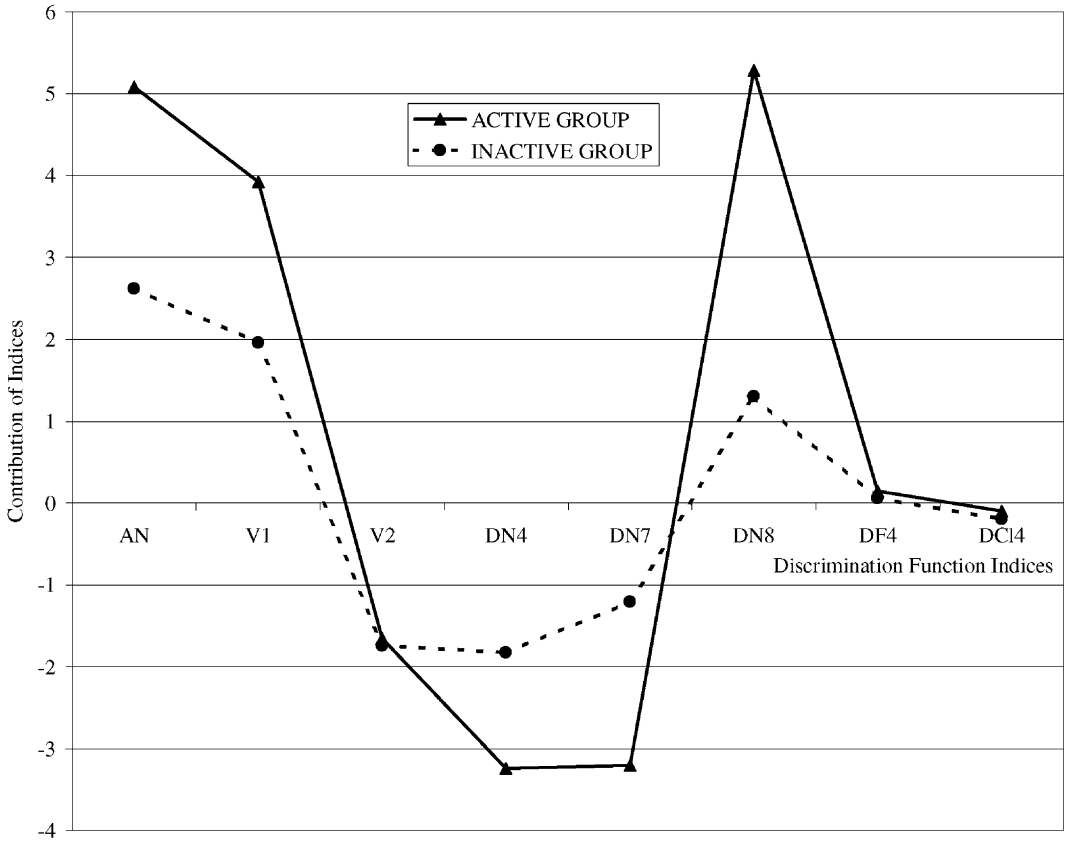


Fig. 3. Average contribution of indices to the discriminant function for active and inactive molecules groups.

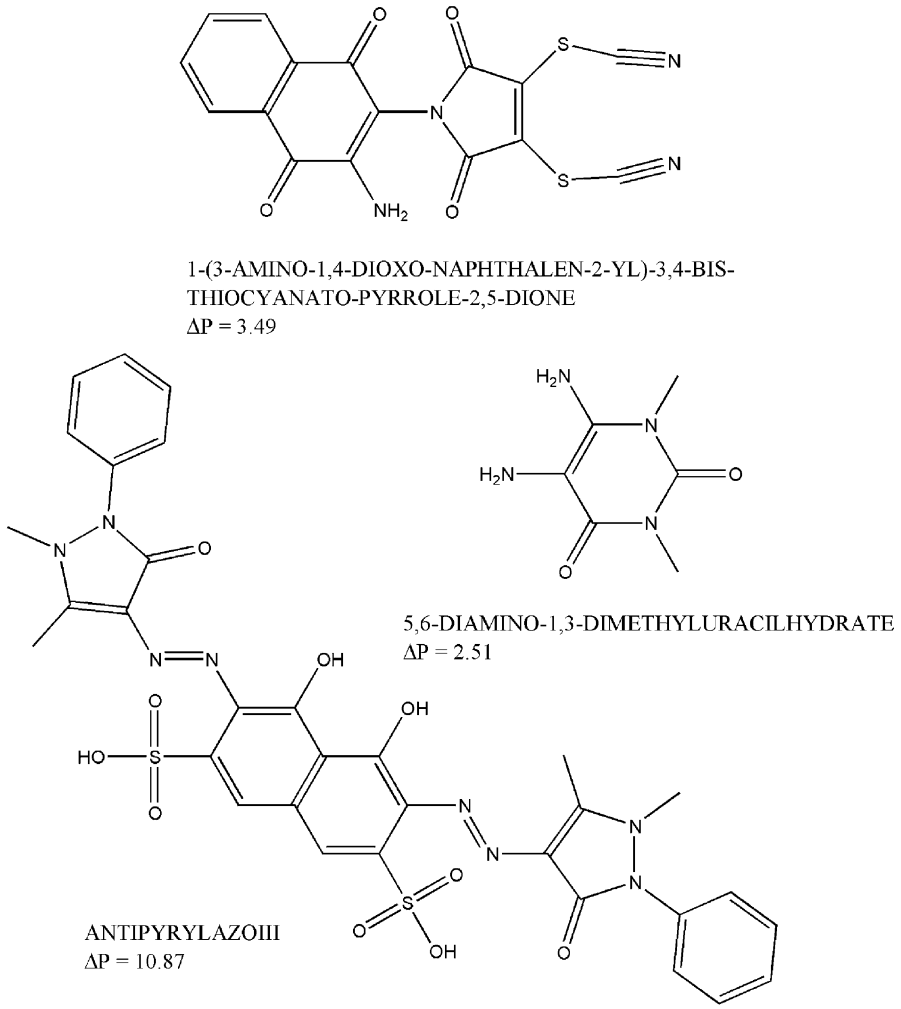


Fig. 4. Chemical structures and $\Delta P$-values of three theoretical antibacterial compounds.

and negative values for inactive compounds (with a maximum value of $\Delta P = -3$, approximately), in both groups of discrimination and the test groups. The values calculated for the discriminant function and the corresponding classification appear in Tables 3–6. However, the selection of active molecules with $\Delta P > 0.5$ can be considered as a contribution to the correct discrimination.

Fig. 3 shows the contribution made by each index as the product of the average index value and its coefficient in the discriminant function. We can therefore say that the indices $V^2$, $D^{F4}$ and $D^{Cl4}$ make the same contribution to both active and inactive groups. Indices $D^{N4}$ and $D^{N7}$ make a negative contribution to both groups (active and inactive), and indices $A^N$, $V^1$ and $D^{N8}$ show a very marked positive contribution to the active group. This demonstrates the importance of the presence of N atoms ($A^N$ index), branching ($V^1$ index) and the size of the molecule ($D^{N8}$ index) in relation to the antibacterial activity.

These topological indices were determined for a large database of compounds without known therapeutic activity (Sigma Aldrich catalogue) and the molecules were classified as active or inactive by applying to them the discriminant function. We have selected as theoretical compounds with antibacterial activity those that show $\Delta P$-value higher than 0.5. Fig. 4 shows the selected compounds with the predicted values for $\Delta P$.

## 4. Conclusions

We use a set of topological descriptors as simple integers applied to individual atoms and bonds in molecules. These indices constitute a contribution to the use of molecular descriptors in QSAR studies.

The discriminant function obtained in the LDA allows the classification of the compounds in actives and inactives with a high percentage of accuracy. The PDD constitutes a valuable tool in discriminating and searching for new lead drugs. By means of this discrimination function we have selected new antibacterial candidates among the structures without known therapeutic activity of a chemical compounds database.

These results verify the discriminative ability of the topological descriptors proposed and suggest that it constitutes a simple tool for QSAR studies and selection of chemical structures which can become new antibacterial drugs.

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