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3D QSAR Markov model for drug-induced eosinophilia—theoretical prediction and preliminary experimental assay of the antimicrobial drug G1

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Abstract—The application of 3D-MEDNEs as a novel alternative technique to reduce the use of animal experimentation in toxicology in the early stages of medicinal chemistry research has been extended from agranulocytosis to chemically induced eosinophilia. Firstly, a heterogeneous series of organic compounds, which are classified either as eosinophilia inductors or noninductors, was collected. A linear discriminant analysis was subsequently used to obtain a QSTR that gave rise to a very good classification of 91.82% (110 chemicals within training series). Eosinophilia inductors (88.89%) composed the first group while the other one contained only harmless compounds (97.37%). The total predictability (88.1%) was tested by means of an external validation series (42 compounds). The model correctly classifies 88.89% of harmless compounds and 87.5% of toxic ones. Finally, comparison of predicted versus experimental results for G1 [2-bromo-5-(2-bromo-2-nitroethenyl)furan, which is a promising antibacterial–antifungal compound] illustrates the practical application of the method. A dose-dependent study of G1 (9.8–185.6 mg/Kg) at 48, 72 and 96 h after oral administration in rats is reported here for the first time. The study has shown that G1 does not affect the murine eosinophils count under these conditions—a situation in total agreement with the model prediction.

1. Introduction

During the fall of 1989, an epidemic of a new disease occurred in the USA. The illness was characterized by blood eosinophilia (raised number of eosinophils, a kind of white cell) and myalgia (severe muscle pain). This disease was termed Eosinophilia–Myalgia Syndrome (EMS). As a consequence of the relatively widespread propagation of the disease, a national surveillance program was initiated by the US Center for Disease Control. The origin of the disease was determined to be strongly related to chemically contaminated tryptophan-containing commercial products. On 11th November 1989, the US Food and Drug Administration (FDA) issued a nationwide warning advising consumers to discontinue the use of tryptophan food complements. The FDA subsequently requested a nationwide recall of all tryptophan sold over the counter. The removal of tryptophan from consumer markets led to a rapid fall in the number of new cases of EMS. Nevertheless, >1500 people were affected by the illness and 37 deaths have so far been attributed to EMS.[1]

The case outlined above illustrates the importance of the study of the relationship between chemicals that are widely consumed and the adverse effects that they may have. Clinically significant adverse effects include blood dyscracias such as mild leukocytosis, leukopenia and eosinophilia and these may occur with organic chemicals such as food supplements and drugs like antipsychotic, antibacterial, antiviral, antithyroid, anticancer, and other medications.[2]

Unfortunately, the adverse effects of drugs are often detected after the drug is introduced into the market or in

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phase III clinical trials. In both cases there is a negative effect on human health, laboratory animals are sacrificed and significant time, and resources are required. In this context, it is natural to consider the necessity for alternative techniques that could predict the untoward effects of a drug on the basis of its chemical structure in the early stages of drug development. In this sense, QSAR/QSTR (quantitative structure activity/toxicity relationships) methods, specifically those based on calculation indices that are not particularly time-consuming, appear to be promising approaches. QSAR/QSTR approaches may in turn help medicinal chemists to rationally select, prior to synthesis, the chemicals with the best prospects to be effective and safe. Regrettably, in spite of the large number of molecular descriptors available, there is a high diversity of toxicological properties to be studied and many have not been investigated until now.[3–17]

In this context, our group has elsewhere introduced different models based on the theory of Markov's chains (MC).[18] The method codifies electron distribution and molecular connectivity. This method termed Markovian Chemicals In Silico Design (MARCH-INSIDE)—has demonstrated its flexibility in many different problems related mainly to bioinformatics and medicinal chemistry. One of the applications in bioorganic and medicinal chemistry was the prediction of fluckicidal activity in novel drugs (flukes are tiny intestinal parasites). In another application in medicinal chemistry, the MARCH-INSIDE approach was applied to the fast-track experimental discovery of novel anticancer compounds. Additionally, promising results were found in the modeling of the interaction between drugs and the HIV-packaging-region RNA in the field of bioinformatics. An alternative formulation of our approach in terms of negentropies gives a more physical sense to our models for drug–RNA interaction. The prediction of the biological activities of peptides and NMR shifts in proteins are problems that can also be addressed by the present approach. A further application in medicinal chemistry involved the design of novel anticoccidial compounds. Codification of chirality and other 3D structural features constitutes another advantage of this method. This last quality in particular allowed the estimation of drug-induced agranulocytocis prior to the synthesis of the compounds themselves.[19–30]

The latter study can be considered as the direct predecessor of the present research and constituted the first report of a method to predict chemically induced blood dyscracias. In this context, QSTR for other drug-induced blood dyscracias may be considered as an orphan branch of preventive QSAR/QSTR studies in medicinal chemistry. In this sense, chemically induced eosinophilia was selected as a subject to expand our study. Additionally, we will illustrate the application of the present method by making both theoretical and experimental preliminary demonstrations of the harmless characteristics of G1 in relation to chemical-induced eosinophilia. G1 is a promising antibacterial–antifungal vinylfuran derivative introduced by the *Chemical Bioactives Center*.[31]

2. Materials and methods

2.1. 3D Markovian chemicals 'in silico' design (3D MARCH-INSIDE)

The MARCH-INSIDE methodology uses MC to codify information about molecular structure. This procedure considers as states of the MC the external electron layers of any atom core in the molecule (valence shell). The method solves the problem of time-dependent electron distribution in the molecule. In this way, the method uses the vector of probabilities ${}^{A}\Pi_0$ and the stochastic matrix ${}^{1}\Pi$ to codify the electron distribution during the early stages of the process of molecule formation. The elements of ${}^{A}\Pi_0$ are the absolute probabilities ${}^{A}\pi_0(j)$ with which each atom releases its own electrons to form the molecule at the initial time t_0. On the other hand, the elements of ${}^{1}\Pi$ are the transition probabilities ${}^{1}\pi_{ij}$. These values are the probabilities with which electrons move from a specific atom a_i to other atom a_j at the first interval of time t_1 after the interaction of atoms to form the molecule:[18–30,32]

$$ {}^{A}\pi_0(j) = \frac{\chi_j \cdot e^{\omega_j}}{\sum_{k=1}^{n} \chi_k \cdot e^{\omega_k}} \quad (1) $$

$$ {}^{1}\pi_{ij} = \frac{\chi_j \cdot e^{\omega_j}}{\sum_{k=1}^{\delta+1} \chi_k \cdot e^{\omega_k}} \quad (2) $$

Where χ_j is the electronegativity of the atom a_j, which is bonded with the atom a_I, and ω_j is a symmetry factor that depends on the 3D environment of the atom (chirality, *Z–E* or axial–equatorial isomerism). One of the more interesting approximations of the method considers the initial distribution of electrons at the time of the collision (${}^{A}\Pi_0$) and the first redistribution of them (${}^{1}\Pi$) determines their subsequent rapid distribution through the chemical bonds (${}^{A}\Pi_k$) until a stationary state (${}^{A}\Pi^{\infty}$) is reached. The elements of the vectors ${}^{A}\Pi_k$ and ${}^{A}\Pi_{\infty}$ are, respectively, the absolute probabilities (${}^{A}\pi_k(j)$) with which electrons reach atom a_j at any increasing time t_k until the stationary state ($t_{\infty} = \infty$). The second approximation considers that such a distribution of electrons is governed by the Chapman–Kolmogorov equations as follows:

$$ {}^{A}\Pi_k = {}^{A}\Pi_0 \times ({}^{1}\Pi)^k \quad (3) $$

The advantages and drawbacks of the method, as well as its theoretical implications, have been widely discussed elsewhere. However, the process of molecule formation can be summarized in the following steps:

1. An interaction takes place between atoms at time t_0 in which they release the electrons with a probability ${}^{A}\pi_0(j)$ (1) proportional to its own electronegativity.
2. The electrons immediately pass from the original atom a_i to another atom a_j with a probability ${}^{1}\pi_{ij}$ (2).

3. The electrons then continue their distribution until they reach the stationary state according to Chapman–Kolmogorov equations (3).[18–30]

2.2. 3D Markovian electronic delocalization entropies (3D-MEDNEs)

As discussed previously, the $^{1}\Pi$ matrix depends on the connectivity and 3D chemical structure. The present approach therefore allows us to explore the potentialities of the MC as source of simple molecular descriptors based on the use of the concept of entropy. These molecular descriptors were defined in our previous work as 3D-MEDNEs (3D Markovian Electronic Delocalization Entropies). The calculation of the 3D-MEDNEs is very simple from the absolute probabilities with which electrons reach a specific atom with time, $^{A}\pi_{k}(j)$. In other words, the entropy involved in the movement of electrons in a time $t_k = k$ through k chemical bonds to reach atom j, ($\Theta_k(j)$). The sum of the $\Theta_k(j)$ values for all n atoms in the molecule or a specific time k are the 3D-MEDNEs used here as total molecular descriptors:[30]

$$\Theta_k = -\sum_{j=1}^{n} \Theta_k(j) = -k_B \sum_{j=1}^{n} [{}^{A}\pi_k(j)] \cdot \ln[{}^{A}\pi_k(j)] \quad (4)$$

Natural logarithm expressions are used instead of base 2 expressions (as used in Shannon's expression) and this is also multiplied by k_B (the Boltzmann constant). This change only involves a change of scale from bits (more common in information theory) to kJ K^{-1}, which is more familiar to the chemist, and in each case the physical meaning remains the same.[33]

The calculation of $\Theta_k(j)$ for any organic or inorganic molecule was implemented in a preliminary version of our software MARCH-INSIDE. This software has a graphical interface that makes it user friendly for medicinal chemists. Input of the chemical structure is carried out by directly drawing of the molecular graph in the software draw mode. Clicking in an upper dynamic array, which contains the labels for the different groups of the Periodic Table, selects the active atom symbol. The calculation option can then be selected to proceed with the calculation of molecular indices.[34]

2.3. Statistical analysis

As a continuation of the previous sections, it is possible to develop a simple linear QSTR using the MARCH-INSIDE methodology and Linear Discriminant Analysis (LDA):

$$\mathrm{EOS} = b + b_0\Theta_0(j) + b_1\Theta_1(j) + b_2\Theta_2(j) + \ldots\ldots + b_k\Theta_k(j) \quad (5)$$

Here, b_k are the coefficients of the discriminant function sought by means of LDA. The model deals with the discrimination of eosinophilia inductors from nontoxic compounds. Tree Joining Cluster Analysis was previously used to design the training and predicting sets. Single distance was used as the clustering method and Euclidean distance selected as the linkage distance. The Activity was codified by a dummy variable (EOS). This variable indicates either the presence (EOS = 1) or absence (EOS = −1) of activity upon pharmacological treatment with the drug. Forward stepwise was fixed as the strategy for variable selection. The first 6 molecular descriptors and the 15th one were used to develop the QSTR (a total of 7 molecular descriptors).[35,36]

The quality of the model was determined by examining Wilk's λ statistic, Mahalanobis squared distance (D^2), Fisher ratio (F) and the p-level (p). The percentage of good classification was assessed along with the proportion between the cases and variables in the equation or variables to be explored. These comparisons were made in order to avoid over-fitting or chance correlation. Validation of the model was corroborated by means of an external prediction series; these compounds were never used to develop the classification function.

The performance of 3D MEDNEs in modeling chemically induced eosinophilia was compared with that of other molecular invariants derived from the $^{1}\Pi$ matrix. These descriptors ($^{SR}\pi_k$) are the sum of the probabilities in the main diagonal of $^{1}\Pi$. The absolute values of the series of $^{SR}\pi_k$ increase in time t_k with the probabilities $^{k}\pi_{ij}$ ($i = j$) of electrons returning to a given atom. The comparison may prove interesting because of the previous application of these self-return probabilities $^{SR}\pi_k$ in other QSAR studies.[37,38]

2.4. Chemical data and laboratory animals

A general data set composed of 152 organic chemicals was considered. This original set was split through a tree joining cluster analysis in order to design 2 series' of eosinophilia-causing compounds of chemicals and 2 series' of nontoxic materials. One series of each kind—containing 72 eosinophilia inductors and 38 nontoxic compounds—was used as a training set. The remaining chemicals were used in the cross validation. The eosinophilia-causing effect of each chemical was verified by different references, taking into consideration contradictory opinions. The biological activity and chemical structure of each of the compounds was extracted from different databases.[39–44]

2.5. Biological assay

Sufficient quantities of G1 for biological assays were purchased (analytical grade) from the Chemical Bioactives Centre. Differential counting of eosinophils was carried out as recommended in the literature. Healthy Sprague Dawly rats selected as the biological model were purchased from the 'Centro Nacional de Animales de Laboratorio (CENPALAB)', Cuba. Quarantine, labeling, acclimatization, and good maintenance conditions of animals were strictly obeyed. Animals were 6 to 8 weeks old and weight in the range of 150–200 g being quarantine period 7 days long. In the design of the experiment were used 70 male rats of line S/D. A total of 9 animals per group were distributed in 7 groups

including: (1) positive control (5 mg/Kg of Cyclophosphamide), (2) 185.6 mg/Kg of G1, (3) 61.8 mg/Kg of G1, (4) 23.4 mg/Kg of G1, (5) 12.3 mg/Kg of G1, (6) 9.8 mg/Kg of G1, and (7) negative control (Migliol). Each one of the groups was monitored at 48, 72, and 96 h following the technique as reported in the literature to carry out eosinophils count.[30,39,41,45–47]

3. Results and discussion

3.1. 3D-MEDNEs-based QSTR modeling of eosinophilia using LDA

Drug-induced injuries of the blood are termed blood dyscracias. Many authors refer to the four major types of Drug-Induced Blood Dyscracias (DIBD) as hemolytic anaemia, thrombocytopenia, agranulocytosis, neutropenia and aplastic anaemia. A consensus conference proposed standardized definitions and general criteria to assess the cause of DIBD. Several terms are used to refer to abnormally low numbers of White Blood Cells (WBC). The broadest description, leukopenia, simply describes a total WBC count of <3000/mm^3. Granulocytopenia describes a granulocyte count (in human beings) of 1500/mm^3 (including eosinophils and basophils) while Neutropenia refers to a neutrophils count (segmented polymorphonucleocytes and band forms) of <1500/mm^3. Agranulocytosis is defined as a severe form of Neutropenia with a total granulocyte count <500/mm^3. In the present work we only focused our attention on raised eosinophils count (eosinophilia).[30,39,41,46]

On the other hand, the application of chirality encoding and/or electronegativity weighted molecular descriptors has focused the attention of researchers on QSAR. Very interesting examples include the work developed by Marrero-Ponce et al.[48] and Julián-Ortiz et al.[49] However, applications to predict the hematology related side effects of drugs are not common. In the study described here, we focused our attention on modeling eosinophilia with MARCH-INSIDE entropies. The first step in this process was the design of the training and predicting series'. The use of a relatively large data series gives rise to

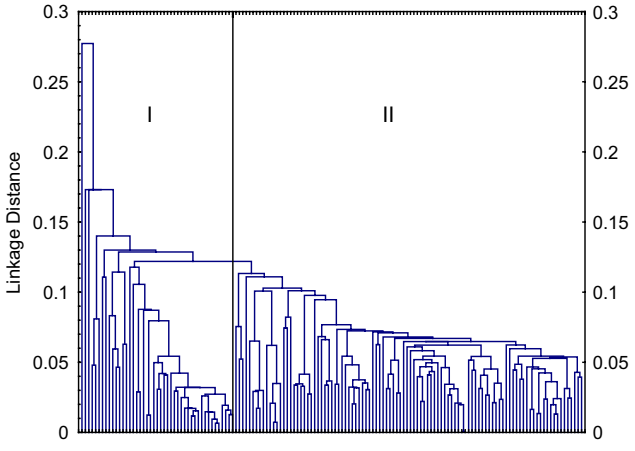


Figure 1. Results of the tree joining cluster analysis.

Table 1. Eosinophilia inductors, names, and posterior probabilities

Name	ΔP%
Eosinophilia inductors in training series	
Allopurinol	−98.62
Alprazolam	91.42
Aminosalicylic	−78.00
Amoxicillin	94.12
Ampicillin	92.43
Atenolol	96.89
Bentazepam	87.44
Benzylpenicillin	89.58
Betaxolol	98.26
Bromazepam	71.64
Camazepam	99.12
Capreomycin	99.98
Carbamazepin	76.02
Carindacillin	99.72
Carteolol	97.16
Cefalexin	91.78
Cefalotin	94.06
Cefamandole	99.14
Cefapirin	97.67
Cefazolin	97.45
Cefoxitin	95.08
Celiprolol	99.81
Chlorpromazine	96.64
Cilastatin	95.53
Cilazapril	97.05
Cloxacillin	97.58
Clozapine	99.62
Dapsone	79.67
Diazepam	86.26
Diethylcarbamazine	57.30
Floxacillin	97.86
Flufenazine	99.99
Flunitrazepam	95.77
Gemfibrozil	83.82
Haloperidol	95.64
Hydralazine	−60.34
Ketazolam	98.85
Labetalol	98.27
Librium	91.35
Loprazolam	99.93
Lormetazepam	91.62
Methicillin	96.18
Nafaline	98.27
Nalidixic acid	64.29
Naproxen	67.49
Niridazole	−54.19
Nitrazepam	92.06
Oxacillin	97.45
Oxprenolol	97.52
Penicillamine	−92.05
Penicillin V	93.31
Pentostatin	78.84
Perindopril	99.55
Phenantoin	−2.42
Pinazepam	92.60
Piperacetazine	99.85
Prontosil	95.70
Quazepam	95.05
Quinapril	99.87
Sulfacetamide	27.64
Sulfamethazine	93.48
Sulfamethoxypyridazine	84.11
Sulfanilamide	−66.84
Sulfapyridine	75.25
Sulfathiazol	46.21

Table 1 (*continued*)

Sulfisoxazol	89.26
Sulfoxone	98.99
Thioridazin	99.67
Ticarcillin	99.02
Trifluoroperazine	98.75
Zalcitabine	−5.44
Zopiclone	99.60
Eosinophilia inductors in predicting series	
Bisoprolol	98.48
Brotizolam	94.50
Carbenicillin	94.83
Carbocysteine	−77.33
Cefradin	94.14
Ceftriaxone	99.55
Clobazam	88.65
Diazoxide	−48.80
Dicloxacillin	97.70
Fenbufen	90.26
Feneticillin	94.82
Flurazepam	99.59
Isoniazide	−90.80
Pimozide	99.92
Piperacillin	99.74
Prazepam	97.32
Probucol	99.90
Ramipril	99.87
Sulfadiazine	68.70
Sulfaguanidine	28.84
Sulfamethoxazole	76.12
Timolol	96.00
Tolrestat	92.82
Trimethoprim	87.79

Table 2. Non-toxic chemicals in training and predicting series

Name	ΔP%
Non-toxic chemicals in training series	
Acetaminofen	−67.68
Acetanilide	−72.94
Acetazolamide	−90.95
Amrinone	−78.00
Aspirin	−46.23
Aurothioglucose	−66.74
Benzene	−99.37
Benzene oxide	−99.47
Caffeine	−87.54
Carmustine	−61.55
Chlordane	−41.81
Dacarbazine	−2.64
Dipyrone	−20.18
Flucytosine	−98.82
Hydrochlorothiazid	−21.02
Levodopa	34.96
Lisuride	−70.54
Mechlorethamine	−96.69
Mercaptopurine	−97.95
Metronidazol	−57.59
Nitrofurantoin	−4.85
Nitroglycerin	−79.51
Nitroprusside	−99.46
p-Phenetidine	−29.88
Propafenone	−81.46
Propylthiouracil	−77.34
Pyrazinamide	−98.13
Resorcinol	−97.78
TEPA	−1.12
Tespamine	−9.14
Theophyllin	−90.11
Thiabendazol	−34.38
Thiomalate	−87.07
Toluene	−97.94
Tranylcypromine	−66.18
Vit. B6	−73.36
Vit. C	−87.03
Vit. K (K3)	−61.47
Non-toxic chemicals in predicting series	
Aniline	
Antipirin	
Benclamide	
Benzene	
Bromodeoxyuridine	
Carbimazole	
Chlorambucil	
Fluorouracil	
G 1	
Hydroxyurea	
Isosorbide dinitrate	
Levamisole	
Methimazol	
Mustar vacilic	
Thioguanine	
Thiouracil	
Valproic acid	
Xylene	

the risk of a nonrandom distribution of chemicals in the two sets (training and predicting). This situation could cause an artificial over-predicting problem; that is, a model with much better predictability than training fitting power. One cause of over-fitting is a nonrandom selection of training and predicting series'. To avoid this and other problems we employed cluster analysis as reported by González et al.[50] and Molina et al.[51] Tree Joining Cluster Analysis was used in the work described here. On an ad hoc basis, Euclidean distance was selected as the linkage distance and single linkage as the linkage method.[51] The results of the Tree Joining Cluster Analysis are depicted in Figure 1.

A similar result was obtained when agranulocytosis was studied in the first publication of the present series.[30] In that case, the only limitation in terms of selection for both the training and predicting series compounds was proportionally distributed over the whole domain of the linkage distance. In a similar way, compounds were selected for training and predicting series chemicals from all sub-clusters in Figure 1.

Having designed the training and predicting series it was possible to carry out the Forward stepwise LDA. LDA produces a set of two classification functions that give rise to an efficient separation of 91.82% of 110 chemicals (training series) into two groups when 3D-MEDNEs are used as molecular descriptors. The first group consists of eosinophilia inductors. The other group contains only compounds that do not cause this untoward effect in human beings. The model correctly classifies 88.89% of chemicals belonging to the first group, that is, 64 out of 72 chemicals (see Table 1 for names and resulting probabilities).

The model classifies 97.37% of compounds (see Table 2) in the second group, that is, 37 cases of 38. As usual in most reported LDA-based QSAR, two classification functions were obtained. The difference between these functions is the so-called discriminant function:[37,52]

$$\mathrm{EOS} = 24.273 \times {}^{1}\mathrm{O}_0 - 26.746 \times {}^{2}\mathrm{O}_{15} + 66.891 \times {}^{3}\mathrm{O}_3 - 43.891 \times {}^{4}\mathrm{O}_2 - 27.366 \quad (6)$$

$$N = 110 \quad \lambda = 0.43 \quad F(4, 105) = 34.682$$
$$D^2 = 5.843 \quad p < 0.000$$

Where ${}^{I}\mathrm{O}_k = {}^{I}\mathrm{O}(\Theta_k)$ represents orthogonalization of the entropies Θ_k throughout Randič's procedure prior to LDA and, in the same order of importance (I), the non-orthogonal variables have entered into the model.[53–56] The total predictability was 88.1%, as assessed by means of an external validation series (42 compounds). The model recognizes as toxic 87.5% of these compounds, that is, 21 chemicals out of 24 (see Table 1). Furthermore, the model correctly classifies 88.89% of the harmless chemicals, that is, 16 cases out of 18 (see Table 2). High collinearity between Θ_6 and Θ_{14} for the present data set determined that these descriptors were not used in the development of the QSAR considering that they consequently do not encode additional structural information.

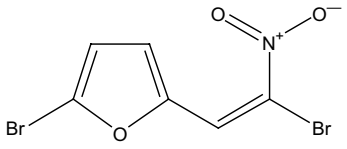
3.2. Comparison with nitrofurantoin, theoretical, and experimental study of G1

The search for eosinophilia inductors may play an important role in detecting this untoward effect in drugs that have been recently introduced into the market. Conversely, the search for harmless compounds may be useful in the early stages of drug discovery. In an effort to exemplify how the present model can be used to guide the search for eosinophilia inductors and/or harmless drugs, the classification of G1 [2-bromo-5-(2-bromo-2-nitroethenyl)furan, $\Delta P\% = -97.73$] was undertaken. Furthermore, an experiment was performed on mice and the results did not show any evidence of the occurrence of eosinophilia in G1-treated groups with respect to control groups. No significant untoward effect was observed on varying the time from administration (see Table 3), which is a very important parameter in detecting some DIBD. In addition, statistical differences in eosinophil counts were not detected after treatment with different drug doses of G1 at 0.05 *p*-level by means of a dependent pair-wise student test. Nevertheless, future phase III studies in human beings will provide the ultimate test in this respect.[30]

We have a special interest in the case of nitrofurantoin due to its close similarity with G1 (both chemicals have a nitro group and a furan ring). In spite of the fact that, eosinophilia may occur under nitrofurantoin treatment, this drug was placed in the noneosinophilia causing group. This decision takes into consideration that eosinophilia occurs within hours to days of the initiation of therapy and is usually resolved within hours after discontinuation of the drug use. This decision was justified elsewhere by the model per se; this compound was predicted to have a fairly low eosinophilia causing effect ($\Delta P\% = -4.85$). This means that the compound is a nonclassified drug and a similar result was obtained when this compound was considered in the group of harmless materials. In any case, neither the specialist nor the model recognizes a serious untoward effect re-

Table 3. Results for the differential count of eosinophils at different times and doses after administration in mouse of G1, vehicle, positive control and negative control solutions

Control groups



	$\Delta U/L\%$[a]		
Time (h)	48	72	96
Control			
Migliol	0.01 ± 0.005	0	0.01 ± 0.005
Negative	0.016 ± 0.01	0.01 ± 0.01	0.016 ± 0.01
Groups treated with G1			
Doses (mg/Kg)			
185.6	0.005 ± 0.007	0.01 ± 0.005	0.005 ± 0.007
61.8	0	0.01 ± 0.001	0
23.4	0.005 ± 0.007	0.06 ± 0.005	0.005 ± 0.007
12.4	0	0	0
9.8	0.003 ± 0.007	0.001 ± 0	0.003 ± 0.007

[a] Difference (arithmetic mean for the respective group) between the eosinophils count after treatment (*U*/*L* (after) with respect to eosinophils count before the treatment *U*/*L* (before) in units (cells) per liter, that is: $\Delta U/L\% = [U/L \text{ (after)} - U/L \text{ (before)}] \times 100$.

lated to eosinophilia in this compound. Hence, the aforementioned structural similarity between G1 and nitrofurantoin provides another reason to support the low capacity of G1 to provoke eosinophilia. Indeed, G1 is recognized by the model as a fairly weak eosinophilia-causing chemical in a similar way to nitrofurantoin ($\Delta P\% = -97.73$ for G1, see Table 2).[57]

4. Concluding remarks

QSAR may be combined with in vitro techniques to develop interesting applications in bioorganic medicinal chemistry, toxicology, and even pharmacokinetics. For instance, Cabrera et al.[58] reported interesting studies on the modeling and experimental corroboration of quinolone absorption. In general QSAR is one of the more interesting applications of topological descriptors and other novel molecular descriptors.[59] In particular, entropy-based descriptors can be very flexible in this respect.[60] Unfortunately, however, almost all useful drugs have specific 3D structural features.[61] For this reason the development of 3D structural feature codification is one of the most fascinating aspects in terms of addressing QSAR/QSTR problems.[62,63] In this sense, the introduction of the 3D-MEDNEs methodology could add another interesting 'weapon' to the 'arsenal' of bioorganic medicinal chemists and toxicologists. Therefore, one of the useful aspects of the work described here is the confirmation of our previous results concerning 3D MEDNEs as a useful tool for QSTR.[30] In addition, another interesting result here is the preliminary demonstration of the harmless characteristics of G1, a promising antibacterial/antifungal drug, with respect to eosinophilia. Nevertheless, the main result reported is the first model introduced in the literature to predict chemically induced eosinophilia. The present results are consistent with others reported recently by Marrero et al., which illustrate the increasing importance of electronegativity-weighted indices in bioorganic medicinal chemistry.[64–66]

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