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# Similarity studies on guanidinium, imidazolinium, and imidazolium cations: Toward new bradykinin antagonists

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*Bradykinin (BK) is a potent nociceptive agent and its antagonists show analgesic activity. In the search for new antagonists of BK, the design of nonpeptidic derivatives with different terminal cations has been considered. Among these new antagonists, the guanidinium cations, which appear not only in the terminal arginine residues of BK but also in several nonpeptidic antagonists, will be substituted by groups with characteristics similar in terms of electrostatic potential, electron density, shape, etc. Several similarity indexes have been calculated for guanidinium, 2-aminoimidazolinium, and 2-aminoimidazolium cations and their corresponding neutral species to design new nonpeptidic BK antagonists. The geometric and electronic characteristics of the molecules were compared by means of: (1) the Carbo index, (2) the Hodgkin index, and (3) a shape similarity index based on the volume of each molecule as defined by a certain electron density. Molecular geometries and energies were optimized by ab initio calculations at the B3LYP/6-311++G** level. The molecular electrostatic potential (MEP) and the electron density (ρ) were then computed in a cubic grid of points around each molecule. These molecular properties were used to calculate similarity indexes with the guanidinium cation or guanidine as the reference molecule in each family. In addition, three-dimensional similarity maps were generated to localize those molecular areas more alike in each of the sets. © 1999 by Elsevier Science Inc.*

*Keywords: similarity, bradykinin antagonist, three-dimensional similarity maps, guanidinium, 2-aminoimidazolinium, 2-aminoimidazolium.*

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## INTRODUCTION

Bradykinin (BK), a linear nonapeptide hormone ($Arg^1$-$Pro^2$-$Pro^3$-$Gly^4$-$Phe^5$-$Ser^6$-$Pro^7$-$Phe^8$-$Arg^9$), elicits many pathophysiological responses including pain and hyperalgesia, and contributes to the inflammatory response[1] (see Figure 1). In about 1980 Regoli and Barabé[2] classified kinin receptors, proposing two subtypes of receptors for BK: the $B_1$ receptors, which are induced and are responsible for hypotension and inflammatory activities; and the $B_2$ receptors, which are the most extensively distributed in plasma and tissues and are responsible for pain.

Two generations of peptidic antagonists of the $B_2$ receptor have been developed, and the most important antagonist found to date is icatibant (HOE 140).[3] This is a decapeptide related to BK, with residues 3, 5, 7, and 8 substituted by nonnatural amino acids that are conformationally restricted (see Figure 1). It should be noted that in most of the peptidic antagonists that have been prepared there are arginine residues, and therefore guanidinium groups, at both extremes of the peptide.

The first nonpeptidic antagonist of the $B_2$ receptor of BK, published in 1993, was a bisphosphonium linked by a modified amino acid.[4] Over the years, both the nature of the cation groups and the nature of the spacers were modified until the best compound of the series, WIN 64338,[5] was found. Another nonpeptidic compound that has shown antagonistic activity for the $B_2$ receptors of BK is the natural product martinelline[6] (see Figure 1). The most recent advance in the development of antagonists for these $B_2$ receptors has been made by researchers at Fujisawa Laboratories (Tsukuba, Japan), who have published four articles proposing a new family of $B_2$ antagonists totally different from those presently known and that are orally active.[7]

There is great interest in the development of nonpeptidic kinin antagonists because peptidic antagonists are expensive to prepare, difficult to deliver, short-lived *in vivo*, and not orally active. In addition, we are interested in the search for nonconventional analgesics and we have focused on the potential

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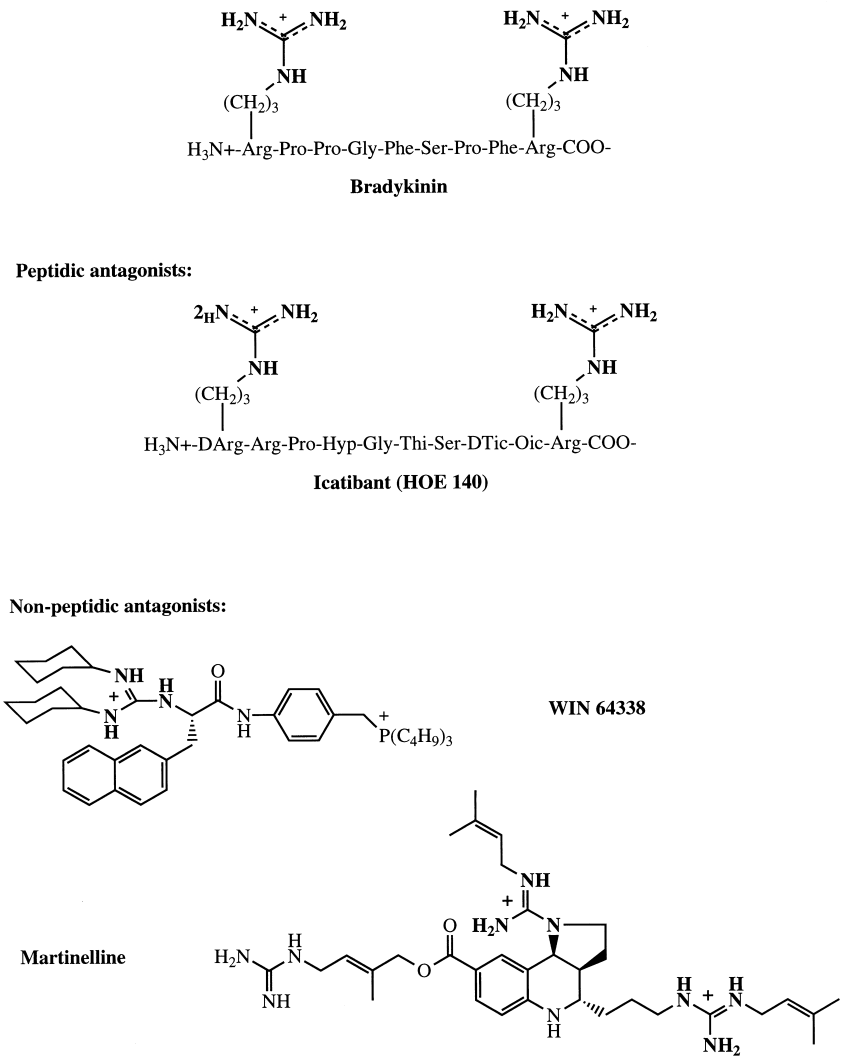



*Figure 1. Chemical formulas of bradykinin and some antagonists (peptidic and nonpeptidic) of its $B_2$ receptor.*

antinociceptive properties of antagonists of the $B_2$ receptor of BK. In both the peptidic and classic nonpeptidic antagonists of this receptor of BK, the most common "motif" (as in BK itself) is the guanidine/guanidinium group. We have therefore considered the preparation of a new family of nonpeptidic antagonists of the $B_2$ receptor of BK, modifying this common motif. In this family the guanidinium cations would be substituted by other groups that would be similar to the guanidinium not only in terms of atomic parameters (distances, angles, and charges) but also in terms of molecular properties such as molecular electrostatic potential (MEP), electron density ($\rho$), and molecular shape. Therefore, we decided to study theoretically the similarity between the guanidinium cation (**1**) and those cations that are more related, such as the 2-aminoimidazolinium (**2**) and 2-aminoimidazolium (**3**) cations (see Figure 2). The study was also extended to the neutral species (**1′**, **2′**, and **3′**; see Figure 2). The similarity of all of these groups could be applied not only to antagonists of BK but also to other compounds, with different pharmacological activities, that also present the guanidine/guanidinium motif in their structures.

The field of molecular similarity has experienced remarkable progress in the last decade.[8] Similarity studies of molecules with potential pharmacological activity have been extensively used for the modeling of new compounds with improved activity.[9] Different approaches have been developed to evaluate this Molecular similarity and we will briefly mention some of the most representative.

The molecular shape analysis theory, developed by Mezey and Arteca, was used to explain some pharmacological activities.[10] In this approach the molecular shape was defined by a molecular property (MEP, molecular lipophilic potential [MLP], $\rho$, etc.) calculated on a molecular surface. A topological analysis was then carried out, providing a certain set of indexes.

Others have been trying to understand similitude in terms of the similarity of atoms within molecules.[11] These authors developed several shape descriptors that involve electron density and that are based on the theory of atoms in molecules as developed by Bader and co-workers.[12]

However, the most widely used formula for the assessment of molecular similarity is probably the Carbo index.[13] This quantum molecular similarity index (QMSI) is determined from the overlap of the same property, originally electron density, in two molecules optimally superimposed. The Carbo

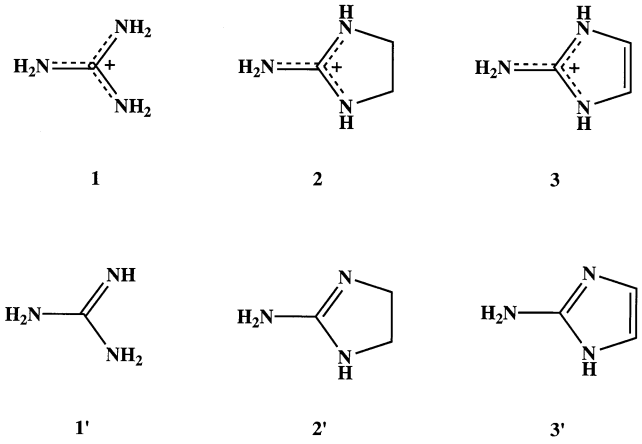



*Figure 2. Structures considered in this study: guanidinium (**1**), 2-aminoimidazolinium (**2**) and 2-aminoimidazolium (**3**) cations and guanidine (**1′**), 2-aminoimidazoline (**2′**) and 2-aminoimidazole (**3′**).*

index is sensitive to the shape of the property rather than its magnitude. In an attempt to correct this, Hodgkin and Richards proposed the Hodgkin index[14] to increase the magnitude sensitivity of similarity calculations. Carbo *et al.* demonstrated that there is a direct relationship between both QMSIs[15]: $R^2_{AB} = H_{AB}\,(K + H_{AB})^{-1}$, where $K$ is almost a constant.

Other, alternative indexes have been developed for drugs on the basis of the idea that drug similarity is related to the difference in binding energies, which would be proportional to the difference in electrostatic potentials.[16]

In the present study we have used the indexes of Carbo and Hodgkin as well as another index that accounts for the similarity in the volume of the molecules as defined by an isodensity surface. The aim of this work is to determine how similar 2-aminoimidazolium and 2-aminoimidazolinium cations are to guanidinium; the results obtained could be used, for example, in the design of new nonpeptidic antagonists for the $B_2$ receptors for BK.

## COMPUTATIONAL METHODS

### *Ab initio* calculations

The calculations have been performed using the Gaussian 94[17] program. All structures have been fully optimized with the 6-311++G**[18] basis set using the hybrid Hartree–Fock/density functional theory B3LYP method.[19] All of the stationary points found were characterized as minima by frequency calculations at the B3LYP/6-311++G** level, all frequencies being real.

The Gaussian 94 program was also used to calculate both the MEP and $\rho$ on a three-dimensional grid around each molecule. This grid was similar for all of the structures and it extended 5 Å from the largest molecule in each direction. A total number of 125,000 points for each grid was chosen (50 in each of the $x$, $y$, and $z$ axes), giving a density of 37.56 points per Å$^3$.

### Similarity indexes

In the present study, similarity between the different cations (and also the different neutral species) has been calculated by means of the following indexes:

1. The numerical solution of the Carbo index[13]: The molecular similarity of two molecules A and B ($R_{AB}$) is calculated with Eq. (1) on the basis of the structural properties $P_A$ and $P_B$ of these two molecules:

$$R_{AB} = \frac{\Sigma P_A P_B}{(\Sigma P_A^2)^{1/2}(\Sigma P_B^2)^{1/2}} \qquad (1)$$

   where $P_N$ ($N$ = A or B) is the value for the MEP or for $\rho$, calculated for each molecule at the same point of the three-dimensional grid generated for molecules A and B, which are optimally superimposed. The maximum value of this index is 1, indicating strongest similarity. It should be noted that the original definition of the Carbo index was computed analytically [in Eq. (1) the summation symbols should be changed to integral symbols]. However, in this work this and subsequent indexes have been computed numerically. This is for practical reasons, to allow straightforward computation of the molecular properties on a cubic grid and the generation of the three-dimensional maps.
2. The correction made by Hodgkin to the Carbo index in order to make it more sensitive to the magnitude of the property $P$, as expressed by Eq. (2):

$$H_{AB} = \frac{2\Sigma P_A P_B}{\Sigma P_A^2 + \Sigma P_B^2} \qquad (2)$$

   where again $P_N$ ($N$ = A or B) represents the value for the MEP or for $\rho$ for each molecule, and the maximum value of this index would be 1, when the values of the property in two molecules are the same.
3. A shape similarity index based on the volume of each molecule as defined by an isodensity surface (0.001 $e$/a.u.$^3$),[20] defined by Eq. (3):

$$S_{AB} = \frac{V_{AB}}{\min(V_A, V_B)} \qquad (3)$$

This index evaluates the similarity by counting the number of grid points that are inside the individual and common isodensity volumes in each molecule. The maximum value for this index would be 1 in the case of total similarity between two molecules.

As mentioned above, the Carbo and Hodgkin indexes are related,[15] and thus they cannot be considered as independent variables of the same equation. Then, two total similarity indexes can be calculated as the addition of the Carbo or Hodgkin index and the volume index for molecules A and B [Eqs. (4) and (5), respectively]:

$$TR_{AB} = R_{AB} + S_{AB} \qquad (4)$$

$$TH_{AB} = H_{AB} + S_{AB} \qquad (5)$$

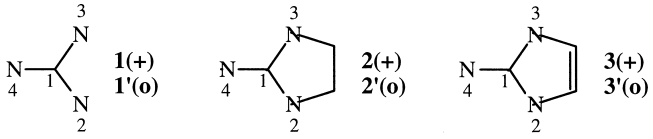
The maximum value for these two indexes would be 2 in the case of total similarity between molecules A and B.

## RESULTS AND DISCUSSION

### Geometry

Table 1 shows some calculated geometric parameters such as the interatomic bond distances and bond angles of the common N—C(—N)—N moiety for the six molecules.

**Table 1. Calculated geometric parameters for the six molecules studied**




| | C-1–N-2 | C-1–N-3 | C-1–N-4 | N-4–C-1–N-2 | N-4–C-1–N-3 | N-3–C-1–N-2 |
|---|---|---|---|---|---|---|
| **1** | 1.335 | 1.335 | 1.335 | 120.0 | 120.0 | 120.0 |
| **2** | 1.337 | 1.337 | 1.331 | 124.7 | 124.7 | 110.7 |
| | (0.002) | (0.002) | (0.004) | (4.7) | (4.7) | (9.3) |
| **3** | 1.346 | 1.346 | 1.339 | 126.6 | 126.6 | 106.7 |
| | (0.011) | (0.011) | (0.004) | (6.6) | (6.6) | (13.3) |
| **1′** | 1.392 | 1.279 | 1.398 | 112.0 | 120.6 | 127.4 |
| **2′** | 1.402 | 1.279 | 1.383 | 117.8 | 125.0 | 117.3 |
| | (0.010) | (0.0) | (0.015) | (5.8) | (4.4) | (10.1) |
| **3′** | 1.349 | 1.287 | 1.385 | 121.5 | 126.0 | 112.5 |
| | (0.053) | (0.008) | (0.013) | (9.5) | (5.4) | (14.9) |

Bond distances (angstroms) and bond angles (degrees) of all of the optimized structures [cations (+) and neutral species (o)] were calculated at the B3LYP/6-311++G** level. The differences with respect to guanidinium (for **2** and **3**) or guanidine (for **2′** and **3′**) appear in parentheses.

Similar bond distances are found for the three cations. Among these structures two of the three C–N distances are either equal or similar from one ion to another (~1.34 Å, see Table 1). The differences with respect to the guanidinium cation ranged from 0.002 to 0.004 Å and from 0.004 to 0.011 Å for **2** and **3**, respectively. For the three neutral molecules quite similar distances are found, although not as similar as for the cations. Among these three molecules the three C–N distances are not equal and the differences with respect to guanidine range from 0.0 to 0.015 Å and from 0.008 to 0.053 Å for compounds **2′** and **3′**, respectively.

Regarding the bond angles obtained in the calculations, the variances are much larger but, again, cations are more similar among themselves than are the neutral species (see Table 1). In the case of the charged molecules, bond angles of compound **2** (differences between 4.7 and 9.3°) are more similar to those of compound **1** than to those of compound **3** (differences between 6.6 and 13.3°). These shifts become larger when comparing the neutral molecules, being between 4.4 and 10.1° for compound **2′** and between 5.4 and 14.9° for compound **3′**.

Therefore, it seems that in terms of geometry compounds **2** and **2′** are more like models **1** and **1′** than are unsaturated molecules **3** and **3′**.

## Charges

Mulliken atomic charges have been collected in Table 2 for all of the structures studied. As with the geometric results, atomic charges are more similar for the charged species than for the neutral species. The differences obtained with respect to the model molecules (**1** and **1′**) range from 0.011 to 0.144 *e* and from 0.003 to 0.146 *e* for ions **2** and **3**, respectively. For the neutral molecules these differences range from 0.027 to 0.168 *e* and from 0.011 to 0.336 *e* for compounds **2′** and **3′**, respectively.

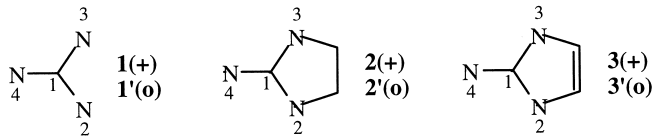
It is not possible to calculate directly the charges on atoms in a molecule, and so a large number of schemes have been proposed for distributing electrons between the atoms in a molecule. Mulliken atomic charges have been the most frequently used for many years, but a number of alternative methods have been developed. One of the most successful has been the CHELPG method,[21] in which molecular atomic charges are extrapolated from the MEP. Thus, we have computed the CHELPG atomic charges for the six structures. The results are gathered in Table 2. By using this method the atomic charges are, in general, more similar between the neutral species than between the charged species. Within each set the differences obtained for the models range from 0.052 to 0.476 and from 0.015 to 0.701 for **2** and **3**, respectively, and from 0.044 to 0.229 and from 0.006 to 0.273 for **2′** and **3′**, respectively.

Thus, regarding atomic charges, even though the results obtained show a high similarity, 2-aminoimidazolinium cation (**2**) and 2-aminoimidazoline (**2′**) seem to be more similar to structures **1** and **1′**, respectively.

## Similarity indexes

Geometric and charge parameters give a partial idea of the similarity between two molecules. To obtain a broader similarity measurement, we have calculated a number of parameters that take into consideration general properties of molecules, including molecular electrostatic potential (MEP) and electron density ($\rho$). As we described in Computational Methods, the indexes chosen for this study were the Carbo index ($R_{AB}$) and the modification made by Hodgkin ($H_{AB}$). Both indexes consider the property (MEP or $\rho$) calculated on a cubic grid of points around the molecules. Further, the volume index $S_{AB}$ (as defined by an isodensity surface of 0.001 *e*/a.u.$^3$) and the total similarity indexes $TR_{AB}$ and $TH_{AB}$ (as described above) were calculated. All of the indexes were computed by taking the guanidinium cation (**1**) and guanidine (**1′**) as model compounds, and the molecules were optimally superimposed on the models. The results are shown in Table 3.

**Table 2. Mulliken and CHELPG atomic charges for the six molecules studied**




| | C-1 | N-2 | N-3 | N-4 |
|---|---|---|---|---|
| | | **Mulliken atomic charges** | | |
| **1** | +0.352 | −0.398 | −0.398 | −0.398 |
| **2** | +0.363 | −0.254 | −0.254 | −0.365 |
| | (0.011) | (0.144) | (0.144) | (0.033) |
| **3** | +0.289 | −0.252 | −0.252 | −0.395 |
| | (0.063) | (0.146) | (0.146) | (0.003) |
| **1′** | −0.087 | −0.320 | −0.364 | −0.346 |
| **2′** | +0.081 | −0.205 | −0.239 | −0.319 |
| | (0.168) | (0.115) | (0.125) | (0.027) |
| **3′** | +0.249 | −0.354 | −0.353 | −0.432 |
| | (0.336) | (0.034) | (0.011) | (0.086) |
| | | **CHELPG atomic charges** | | |
| **1** | +1.148 | −0.999 | −0.999 | −0.999 |
| **2** | +0.771 | −0.523 | −0.523 | −0.947 |
| | (0.377) | (0.476) | (0.476) | (0.052) |
| **3** | +0.672 | −0.298 | −0.298 | −0.984 |
| | (0.476) | (0.701) | (0.701) | (0.015) |
| **1′** | +0.995 | −0.973 | −0.938 | −0.967 |
| **2′** | +0.878 | −0.744 | −0.752 | −0.923 |
| | (0.117) | (0.229) | (0.186) | (0.044) |
| **3′** | +0.822 | −0.700 | −0.338 | −0.961 |
| | (0.173) | (0.273) | (0.186) | (0.006) |

Mulliken and CHELPG atomic charges were obtained for all of the optimized structures [cations (+) and neutral species (o)] and calculated at the B3LYP/6-311++G** level. The differences with respect to guanidinium (for **2** and **3**) or guanidine (for **2′** and **3′**) appear in parentheses.

**Table 3. Global similarity indexes calculated for the six molecules studied**

| | MEP | | $\rho$ | |
|---|---|---|---|---|
| | **2** | **3** | **2** | **3** |
| $R_{AB}$ | 1.00 | 1.00 | 0.77 | 0.77 |
| $H_{AB}$ | 1.00 | 1.00 | 0.74 | 0.75 |
| $S_{AB}$ | 0.99 | 0.98 | 0.99 | 0.97 |
| $TR_{AB}$ | 1.98 | 1.97 | 1.76 | 1.74 |
| $TH_{AB}$ | 1.98 | 1.97 | 1.73 | 1.71 |
| | **2′** | **3′** | **2′** | **3′** |
| $R_{AB}$ | 0.98 | 0.86 | 0.77 | 0.76 |
| $H_{AB}$ | 0.98 | 0.86 | 0.74 | 0.74 |
| $S_{AB}$ | 0.98 | 0.96 | 0.98 | 0.96 |
| $TR_{AB}$ | 1.96 | 1.82 | 1.75 | 1.72 |
| $TH_{AB}$ | 1.96 | 1.82 | 1.72 | 1.70 |

Global similarity indices were calculated for the structures (cations and neutral species) and optimized at the B3LYP/6-311++G** level. The model molecules were guanidinium (**1**) for the cations and guanidine (**1′**) for the neutral species.

Since MEP can reach very high or even infinite values when computed in the vicinity or at the exact atomic positions, the corresponding $R_{AB}$ or $H_{AB}$ could possess an indeterminate or infinite value. To solve this problem, only those points of the cubic grid around the molecule that are outside the volume defined by an isodensity surface of 0.001 *e*/a.u.$^3$ were considered for both Eqs. (1) and (2). When $P_N = \rho$, we followed the same methodology.

For the cations, when the calculated property is the MEP, the values are 1.00 for $R_{AB}$ and $H_{AB}$, range from 0.98 to 0.99 in the case of $S_{AB}$, and reach 1.97 to 1.98 in the case of the total indexes ($TR_{AB}$ and $TH_{AB}$). These values would indicate that both 2-aminoimidazolinium (**2**) and 2-aminoimidazolium (**3**) cations are both identical to **1**. Yet, these high $R_{AB}$ and $H_{AB}$ similarity values can be the result of the shape of the MEP in charged molecules. In these molecules the MEP has a maximum over the molecule and it diminishes quickly as one moves away from it, maintaining its positive value, whereas in neutral molecules the MEP surface is smoother with positive and negative values outside of the molecular van der Waals surface. On the other hand, the shape of the electron density is independent of the charge of the molecule. Thus, when this property is compared, the similarity values obtained are smaller, ranging from 0.74 to 0.77 for $R_{AB}$ and $H_{AB}$, 0.97 to 0.99 for $S_{AB}$ and from 1.71 to 1.76 for $TR_{AB}$ and $TH_{AB}$. Hence, by using electron density it is possible to differentiate between the three cations, and it is found that cation **2** is a little more like **1** than is cation **3**.

In the case of the neutral species (see Table 3), the indexes obtained with both properties (MEP and $\rho$) for compound **2′** (0.98, 1.96 for MEP; and from 0.98 to 0.77, ~1.74 for $\rho$) are more significant than for compound **3′** (from 0.96 to 0.86, 1.82 for MEP; and from 0.96 to 0.74, ~1.71 for $\rho$), which seems rather high in all cases. Thus, from all these indexes and properties it can be concluded that 2-aminoimidazoline (**2′**) is more like guanidine (**1′**) than is 2-aminoimidazol (**3′**).

## Local similarity

The similarity indexes used in the previous section provide a global measurement of the similitude between two molecules. However, sometimes one needs to know how similar specific common parts of two molecules are, independent of the rest of the structure but still considering a molecular property. Hence, using the Carbo index previously mentioned, we have developed three-dimensional similarity maps for two optimally superimposed molecules, using which it is possible to distinguish those parts of the molecules that are more alike than are other parts, based on the values of some molecular properties of both of them.

The construction of these three-dimensional similarity maps is as follows:

1. First, the model molecule and the structure to be compared should be optimally superimposed, with the help of some molecular modeling package (in our case we used SYBYL[22]), and an attempt made to match the parts that are more similar in both compounds.
2. Then, considering each molecule in the orientation of the superimposition and with the help of the Gaussian 94 program, a cubic grid of points is generated around the molecules, similar to how the global indexes are calculated.
3. The corresponding molecular property (MEP or $\rho$) is then calculated for each of the points of the cubic grid for each molecule, using the Gaussian 94 program.
4. Now, the Carbo index is calculated for each point that is part of the common grid (for a certain molecular property, e.g., MEP or $\rho$) and that is outside the isodensity surface as defined by the value of 0.001 $e$/a.u.$^3$. Thus, we will have a cubic grid of points around the two superimposed molecules and each point will have a value of $R_{AB}$.
5. With the help of a molecular modeling program (SYBYL, in our case), it is possible to represent this cubic grid of points around the two superimposed molecules. By assigning a range of colors to different sets of $R_{AB}$ values (which were previously normalized between 0 and 100) we could have a graphic representation of those parts that are more alike than others in the two molecules for a certain molecular property. Those values less than a certain cutoff (i.e., lower or null similarity) were eliminated from the graph in order to make it easier to visualize. This cutoff depends on the molecular property and the structure compared.

Thus, we built these three-dimensional similarity maps to compare the MEP and $\rho$ values of the three cations and also those of the neutral molecules, using as model molecules the guanidinium cation and guanidine. The results obtained are represented in Color Plates 1 and 2 for the MEP of cations and neutral species, respectively, and in Color Plates 3 and 4 for the $\rho$ of cations and neutral molecules, respectively.

When the MEP is compared for the three cations (Color Plate 1), with a cutoff of 50, we observed a large number of points in both maps (1220 points for **1** versus **2**, and 1264 points for **1** versus **3**). This means that many of the points of the cubic grids have $R_{AB}$ values within the limits of that cutoff, indicating a high degree of similarity of **2** and **3** with respect to **1**. In particular, we observed that in both maps the similarity is high (points of green, yellow, and red colors, $R_{AB}$ values between 64.25, 78.50, 92.75, and 100) around the area where the charge is delocalized (common N—C—N moiety). The number of these points is slightly higher in the map corresponding to the superimposition of guanidinium with 2-aminoimidazolinium.

On the other hand, in the maps corresponding to the MEP comparison of the neutral molecules (Color Plate 2) and with a cutoff of 40, the total number of points in each map is smaller than that of the cations (272 points for **1** versus **2**, and 254 points for **1** versus **3**). This means that fewer points have a value of $R_{AB}$ within the limits of that cutoff, and therefore, there is less similarity between the three molecules. In this case, the higher similarity (points of green, yellow, and red colors, $R_{AB}$ values between 56.79, 73.52, 90.26, and 100) is localized on the unsubstituted ═N atom of both rings and the N—H atom of guanidine.

The same methodology was followed to study the similarity by using $\rho$ as the molecular property to compare. A cutoff of 40 was used for both sets. The maps obtained for the cations are represented in Color Plate 3 and for the neutral molecules in Color Plate 4. As with the MEP, the total number of points within the cutoff is larger for the cations (344 points for **1** versus **2**, and 321 points for **1** versus **3**) than for the neutral species (283 points for **1** versus **2**, and 254 points for **1** versus **3**). This means that the cations are more similar among themselves than are the neutral molecules. However, by using this property it was more difficult to find local similarities over a certain atom or small set of atoms. The points with values of high similarity (points of green, yellow, and red colors, $R_{AB}$ values between 49.30, 68.53, 87.77, and 100) were localized all around the N—C(—N)—N moiety (guanidine group) for all of the superpositions (see both Color Plates 3 and 4).

## CONCLUSIONS

The comparison of geometric parameters as distances or angles as well as atomic charges can be used to establish a partial degree of similarity. However, the use of indexes built from molecular properties as MEP or $\rho$ gives a better idea of how alike two molecules are because global properties, rather than independent parts, of the molecules are considered.

Three-dimensional similarity maps can be used to determine the similarity between certain common parts of a set of molecules. These maps are built by considering some molecular property of the two molecules compared, and the similarity index is decomposed in the different areas of the two optimally superimposed molecules. From the results obtained with these maps it can be concluded that MEP is a better molecular property to use when searching for local similarities.

The three cations and the three neutral molecules compared in this study present a high degree of geometric and electronic similarity. However, by analyzing all of the criteria studied here it may be concluded that 2-aminoimidazolinium and 2-aminoimidazoline (**2** and **2′**, respectively) exhibit a better overall molecular similarity to guanidinium and guanidine (**1** and **1′**, respectively) than do the unsaturated derivatives 2-aminoimidazolium and 2-aminoimidazole (**3** and **3′**, respectively).

As a consequence of this study, we have synthesized bis-guanidinium and bis-2-aminoimidazolinium nonpeptidic derivatives, some of which are antagonists of the $B_2$ receptors of BK and also show analgesic activity. Yet, the preparation of bis-2-aminoimidazolinium analogs cannot be set aside and should be carried out in the future.

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