Application of Molecular Topology to the Prediction of the Reaction Yield and Anticancer Activity of Imidazole and Guanidine Derivatives

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ABSTRACT

In this study molecular topology based QSAR has been applied to predict the reaction yield and anticancer activity of 18 imidazole and guanidine derivatives. Four properties were evaluated, namely reaction yield, anti prostatic-cancer activity, anti breast-cancer activity and anti lung-cancer activity. The four models have been validated by both internal and cross validation, and also by randomness tests. The results obtained are in full agreement with the experimental results and confirm the precision, accuracy and robustness of the method followed. After carrying out a virtual screening upon such models, new imidazole and guanidine derivatives with potential anticancer activity are proposed.

Keywords: Anticancer Activity, Imidazole and Guanidine Derivatives, Molecular Topology, Multilinear Regression Analysis, QSAR Analysis

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INTRODUCTION

Cancer is one of the biggest problems concerning health issues that humanity faces. The investigation and search for new active drugs against different tumor cell lines is urgently needed.

The first stage of search usually begins with the synthesis of different organic compounds and its subsequent biological evaluation. The process of organic synthesis attempts to use little polluting and environmentally friendly procedures. For example, using laboratory techniques that eliminate, to the extent possible, the use of organic solvents. This is the case of microwave-assisted synthesis of imidazole and guanidine derivatives (Sondhi, Singh, Roy, Agrawal, & Saxena, 2001). Microwave-irradiation technique provides the necessary energy to guarantee an efficient synthesis, and therefore reduces the reaction time required (Herrero, Kremsner, & Kappe, 2008; Sondhi & Rani, 2008). These compounds have showed anti-inflammatory (Albrecht, Hauser, Laufer, Striegel, & Tollmann, 2008; Gaonkar, Lokanatha, & Suchetha, 2009), anticancer (Courtney, Hay, & Scopes, 2004; Brzozowski, Saczewski, & Slawinski, 2007) and even antimicrobial (Oezden, Atabey, Yildiz, & Goeker, 2005; Hensler, Bernstein, Nizet, & Nefzi, 2006) activities and are widely described in literature.

On the other hand, Quantitative Structure-Activity Analysis, (QSAR), is a very good alternative to classical studies and an important tool for computational chemistry. These methods are based on relationships between chemical structure and experimental properties whether physical, physico-chemical or biological. Various types of formalisms including molecular mechanics, quantum chemistry, similarity/dissimilarity approaches and topological descriptors have been used in this contest (Devillier & Balaban, 1999).

Based on molecular topology, MT, it is possible to identify different structural levels of a molecule by numerical values called topological descriptors. For that goal, the molecule is allocated to a graph where each vertex represents an atom and each edge is a bond between two atoms. From the graph, the topological or adjacency matrix is constructed so that its elements aij take values either zero or non-zero, depending on the existence or absence of a bond between the atoms i and j, respectively (Galvez, Galvez-Llompart, & Garcia-Domenech, 2012).

Further processing of the matrix leads to topological indices that characterize the graph in a quick and straightforward way. These descriptors have been successfully used in the search, selection and design of new active compounds in different therapeutic areas and particularly in that of cancer (Jasinski et al., 2008; Jasinski et al., 2011; Garcia-Domenech, Galvez, de Julian-Ortiz & Pogliani, 2008; Gonzalez-Diaz et al., 2003).

Therefore, the main objective of this study is to obtain QSAR models using topological descriptors. With this in mind, multilinear regression analysis has been applied to achieve a robust QSAR model capable to predict the reaction yield in the synthesis of guanidine and imidazole derivatives as well as the anticancer activity of the derivatives over human cancer cell lines A-549 (lung), MCF-7 (breast) and PC-3 (prostate).

MATERIALS AND METHODS

Analyzed Compounds

In the present study 18 derivatives of guanidine and imidazole have been chosen. These are listed with their corresponding code (3a-5f) in Figure 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Yield</th>
<th>Anticancer Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>74.5</td>
<td>6.7</td>
</tr>
<tr>
<td>3b</td>
<td>82.3</td>
<td>8.9</td>
</tr>
<tr>
<td>3c</td>
<td>69.2</td>
<td>5.6</td>
</tr>
<tr>
<td>3d</td>
<td>78.4</td>
<td>7.8</td>
</tr>
<tr>
<td>3e</td>
<td>63.7</td>
<td>4.7</td>
</tr>
<tr>
<td>3f</td>
<td>85.6</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Table 1 shows the reaction yield and anticancer activity of each compound (Sondhi, Singh, Roy, Agrawal, & Saxena, 2001).

Molecular Descriptors

In this study we have employed constitutional descriptors, connectivity indices and topological charge indices obtained using DESMOL1 software (DESMOL1 software, 2000).
Validation Approaches to Volcanic Explosive Phenomenology
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