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QSAR studies of novel 1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylic acid derivatives and their precursors as antileukaemic agents

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Abstract

In an attempt to find a potent inhibitor of antileukaemic activity, we performed two-dimensional quantitative structure–activity relationship studies. The QSAR models of the 1-(4-methoxyphenethyl)-1H-benzimidazole derivatives were developed by means of utilizing simulated annealing for the purpose of identifying an effective inhibitor. In the present study, the best 2D QSAR model developed had a cross-validated value of $(q^2) = 0.7584$ and a coefficient of determination of $(r^2) = 0.8477$ with partial least squares analysis. The models also suggest that the inclusion of fluorine, chlorine, methyl, and nitro substituents would enhance the antileukaemic activity. The resulting descriptors produced by the QSAR models were used to identify the physico-chemical features relevant to antileukaemic agents.

Keywords: Benzimidazole-5-carboxylic acid; QSAR; K562 cells; CEM cells; Simulated annealing; Partial least squares; Antileukaemic agents

1. Introduction

Recently, multi-target drugs, which are designed as single molecules to modulate multiple physiological targets simultaneously, have increasingly attracted the attention of medicinal chemists [1], and they represent a very promising way to enhance the efficacy and decrease the adverse effects of drugs, especially in the treatment of complex diseases such as cancers, cardiovascular diseases, and neurodegenerative diseases [2,3]. The leukaemias of childhood are common cancers of the hematopoietic system, primarily involving the malignant transformation of lymphoid progenitor cells and, less commonly, the transformation of myeloid progenitor cells [4]. Cancer is now believed to result from the unlimited growth of a given cell [5]. Cancer has been recognized as a disease of aberrant cellular proliferation, with traditional cancer therapies aiming to exploit the proliferation machinery. Cells die in two ways: necrosis and apoptosis. The regulation of apoptosis is crucial for development and sustained health [6]. The dysregulation of apoptosis will result in a variety of clinical disorders, including cancer. The benzimidazole ring displays an important heterocyclic pharmacophore in drug discovery. Compounds carrying different substituents in the benzimidazole structure are associated with a wide range

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of biological activities, including anticancer [7], antiviral [8], antibacterial [9], antifungal [10], anti-inflammatory [11], proton pump inhibitor [12], antioxidant [13], antihypertensive [14] and anticoagulant [15] properties.

Quantitative structure–activity relationship (QSAR) studies are mathematical equations that quantitatively correlate chemical structures with biological activity. These relationship models have been helpful in understanding the influence of molecular properties on the biological activity of different compounds, ultimately providing rational clues for the development of new compounds with desirable biological properties. Because they provide valuable information for molecular design and medicinal chemistry, QSAR studies have been widely used in drug design and discovery [16].

To gain insight into the structural and molecular requirement influencing antileukaemic activity, we herein describe the QSAR analysis of the novel compound 1-(4-methoxyphenethyl)-1H-benzimidazole, focusing on the development of a QSAR models for antileukaemic activity. These results should serve as a guideline in designing compounds with more potent antileukaemic activity.

2. Materials and methods

2.1. Computational details

The computational studies were performed on a computer using HP Windows 7 Home Basic with an Intel® core processor. The molecular structures of the compounds in the data set were sketched using V-life MDS (Molecular Design Suite)™ 3.5 software, supplied by V-life Sciences Technologies Pvt. Ltd., Pune, India [17].

2.2. Obtaining biological data and training and test sets

The QSAR studies were performed using a series of substituted 1-(4-methoxyphenethyl)-1H-benzimidazole analogues reported in the literature [18]. Out of 22 molecules, four molecules were discarded for which the precise data were not available. The biological activities were represented by the IC_{50} divided by the mean IC_{50} in the two tumour cell lines K562 and CEM. The IC_{50} values were converted into the negative logarithm of pIC_{50} values and used as dependent variables in the QSAR analysis. The test compounds were selected considering the structural diversity and wide range of activity within data set. The chemical structures and their biological activities are represented in Table 1. The sphere exclusion method [19] was adopted for division of the training and test data sets comprising 13 and five molecules, respectively, with a dissimilarity value of 1.0, where the dissimilarity value gives the sphere exclusion radius. The compounds in the test set allowed us to use one test compound over four training compounds, thus resulting in a more rigorous validation of the training model. Five compounds, namely, 3, 7, 11, 16 and 20, were used as the test set, while the remaining molecules were used as the training set.

2.3. Structure generation

The molecular structures of all of the molecules were sketched using the 2D builder module within VLife MDS 3.5 software, and the structures were then converted into the 3D space for further analysis. All of the compounds were batch optimized for the minimization of energies and optimization of geometry using Merck Molecular Force Field, followed by adjusting the parameters to include a distance-dependent dielectric constant of 1.0, convergence criterion or root mean square (RMS) gradient at 0.01 kcal/mol Å and an iteration limit of 10,000 [20].

2.4. Descriptor calculation

A large number of theoretical 2D individual descriptors such as Chi, Path-cluster, Element Count, Estate number, Polar surface area, and alignment-independent topological descriptors have been computed from the chemical structures with an aim of identifying the structure/activity relationship of 1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylic acid compounds which would, in turn, predict their biological activity.

The preprocessing of the independent variables (i.e., descriptors) was performed by removing invariable descriptors (constant column), which resulted in a total of 230 descriptors to be used for QSAR analysis. The descriptors having the same or almost the same value, or those that were highly correlated with other descriptors, were removed initially. The various alignment-independent (AI) descriptors [21] were also calculated.

2.5. Cross validation

Models generated by 2D-QSAR studies were cross validated using a standard LOO procedure. The cross validated r^2 (q^2) value was calculated using Eq. (1), where y_i and $\hat{y}_i$ are the actual and predicted activities of the ith molecule, respectively, and y_{mean} is the average activity of all of the molecules in the training set