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3D QSAR *k*NN-MFA studies on 6-substituted benzimidazoles derivatives as Nonpeptide Angiotensin II Receptor Antagonists: A rational approach to antihypertensive agents

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Abstract The present article is an attempt to the 3D QSAR studies for the 40 molecules of 6-substituted benzimidazoles Nonpeptide Angiotensin II Receptor Antagonists by using *k*-Nearest Neighbor Molecular Field Analysis (*k*NN-MFA) combined with various selection procedures. Molecular field analysis was applied for the generation master grid maps derived from the best model has been used to display the contribution of electrostatic potential and steric, hydrophobic field based on aligned structures. Partial least square methodology coupled with various feature selection methods, viz. stepwise (SW), genetic algorithm (GA) and simulated annealing (SA) were applied to derive QSAR models which were further validated for statistical significance and predictive ability by internal and external validation. By using *k*NN-MFA approach, various 3D QSAR models were generated to study the effect of steric, electrostatic and hydrophobic descriptors on Ang II activity. The best model B with good external and internal predictivity for the training and test set has shown cross-validation (q^2) and external validation (pred_r^2) values of 0.8269 and 0.7647, respectively. For this model training and test sets were selected using sphere exclusion method and the descriptors were selected using simulated annealing method. The summary of the

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selected model can be given as: $k = 4$, $r^2 = 0.8753$, F test = 74.643, r^2_se = 0.2143, q^2_se = 0.4365, pred_r^2se = 0.2165 and descriptors at the grid points S_1018, E_563, S_2083, E_1460, E_160, H_2234, H_2491 and H_1146 play an important role in the design of new molecule. Contour maps using this approach showed that steric, electrostatic and hydrophobic effects dominantly determine binding affinities. The information rendered by 3D QSAR models may lead to a better understanding of structural requirements of antihypertensive activity and can help in the design of novel potent molecules.

1. Introduction

The renin–angiotensin system (RAS) is well established as an endocrine system involved in blood pressure (BP) and fluid electrolyte balance. Renin, an aspartyl protease, cleaves angiotensinogen to produce angiotensin I, which is further converted by angiotensin converting enzyme (ACE) to the potent vasoconstrictor, angiotensin II. Since angiotensinogen is the only substrate known for renin and cleavage of angiotensinogen by renin is the rate determining step in the RAS, it is of general consensus that inhibition of renin would be the optimal strategy for the control of hypertension (Stanton, 2003; Rosenberg and Boyd, 1997). Renin, a proteolytic enzyme produced mainly in the juxtaglomerular apparatus of the kidney, acts on the circulating alpha globulin angiotensinogen produced by the liver to form the decapeptide Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe-His-Leu, named angiotensin I. Angiotensin I is relatively inert but is converted to the active octapeptide Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe, named as angiotensin II by angiotensin-converting enzyme (ACE) present in lungs and other organs. Among them, angiotensin-converting enzyme (ACE) inhibitors have been very successful in the treatment of hypertension and congestive heart failure during the last few decades. However, these inhibitors suffer from some side effects such as dry cough and angioedema caused by their nonspecific actions (Chin and Buchan, 1990; Wood et al., 1990). On the other hand, angiotensin II (Ang II) receptor antagonists block the RAS at the Ang II receptor level. This provides a more specific attempt to inhibit the activity of the RAS and has become the main pharmacological approach (Cockcroft et al., 1993). The therapeutic profile of Ang II receptor antagonist is thought to be similar to that of angiotensin converting enzyme (ACE) inhibitors such as captopril, enalapril and lisinopril. In addition, since Ang II receptor antagonist does not affect the metabolism of bradykinin so they may not have the side effect of ACE inhibitors, such as dry cough and angiodema. Computational chemistry prediction of biological activity based quantitative structure–activity relationship (QSAR) substantially increases the potential of work, avoiding time and resource consuming experiments (Dlazand Prado, 2008). The most popular 3D-QSAR methods are comparative molecular field analysis CoMFA (Cramer et al., 1988) and comparative molecular similarity analysis CoMSIA (Klebe et al., 1994). The CoMFA method involves generation of a common three-dimensional lattice around a set of molecules and calculation of the steric and electrostatic interaction energies at the lattice points while the CoMSIA method uses the similarity functions represented by Gaussian (Kubinyi, 1993). Numerous data sets reported in the literature were subjected to QSAR analysis for the purpose of designing novel angiotensin II receptor antagonists (Belvisi et al., 1996; Datar et al., 2004; Kurup et al., 2001; Sharma et al., 2009). Newly reported method *k*-Nearest Neighbor Molecular Field Analysis (*k*NN-MFA) adopts a *k*-Nearest Neighbor principle for generating relationship of molecular fields with the experimentally reported activity. This method utilizes the active analogue principle that lies at the foundation of medicinal chemistry. For the development of 3D-QSAR, molecular field analysis (Ajmani et al., 2006) has been applied to evaluate specific contributions of steric and electrostatic field effects necessary for the activity variation of 6-substituted benzimidazole derivatives. These steric, electrostatic and hydrophobic field descriptors are useful for the better understanding of molecular modeling studies. In the present investigation, three widely used techniques; viz. stepwise (SW) forward variable selection method, genetic algorithm (GA) and simulated annealing (SA) have been applied for descriptor optimization. In the present study, an attempt has been made to formulate 3D-QSAR models using partial least-squares (Hoskuldsson, 1995) methodology. It is expected that such 3D-QSAR molecular modeling studies of 6-substituted benzimidazoles angiotensin II antagonist will provide better tools for rational design of promising antihypertensive activity having greater therapeutic safety and efficacy. Our aim is to utilize these activity data for the development of a valid 3D-QSAR model based on steric, electrostatic and hydrophobic fields that gives a deep insight into structure property activity correlations.

2. Materials and methods

2.1. Biological activity data

A number of 40 compounds 6-substituted benzimidazoles derivatives having angiotensin II antagonist activities were considered in the present study. The angiotensin II antagonist activity data of synthesized 6-substituted benzimidazole derivatives were taken from the reported work (Uwe et al., 1993). Biological activity expressed in terms of IC_{50} was converted in to pIC_{50} ($pIC_{50} = -\log 1/IC_{50}$). Table 1 shows the structure of 40 such compounds along with their biological activity values. 6-substituted benzimidazoles led the systematic variation of several substituents at the benzimidazole ring positions 4–7. Out of these 40 compounds, small aliphatic substituents such as $–CH_3$, $–NH_2$, $–NHCOCH_3$, and $NHCONCH_3$, are attached at 4–7-positions of compounds. The total set of inhibitors was divided into a training set (28 compounds) for generating 3D QSAR models and a test set (12 compounds) for validating the quality of the models. The training set and test set were selected manually by considering the fact that the test-set compounds represent structural diversity and a range of biological activities similar to that of the training set. In addition, the wide range of structural diversity of