STUDIES ON NOVEL NON-IMIDAZOLE H4 RECEPTOR ANTAGONISTS USING GFA AND FREE-WILSON ANALYSIS

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Abstract. The Histamine H4 receptor is expressed mainly on eosinophils and mast cells and has been shown to be involved in the chemotaxis of both the cell types. The receptor is also implicated in the release of IL-16, from CD8+ T cells. This data indicate that the receptor may play a role in inflammatory process. Herein we describe 3D QSAR studies of non-imidazole Indolylpiperazines using GFA and Free Wilson Analysis. For the GFA model, thirteen molecules were used as training set and three as test set to evaluate the external predictability of the equations generated using GFA \( r^2 = 0.650 \) and \( r^2_{\text{pred}} = 0.807 \]. The results indicate that electronic and thermodynamic parameters are major contributors to the activity. The same set of molecules was analyzed using the Free-Wilson analysis and a good correlation was obtained \( r^2 = 0.988 \].

Introduction
Histamine has been shown to play a critical role in several diverse physiological processes. It is the key component in the inflammatory response via activation of the...
Histamine $H_1$ receptor, gastric acid secretion via the Histamine $H_2$ receptor, and mediation of neurotransmitter release in the central nervous system via the Histamine $H_3$ receptor. Recently a forth histamine receptor, the $H_4$ receptor, was identified. It is a 390 amino acid, seven trans-membranes G-protein coupled receptor and is expressed mainly on eosinophils and mast cells and has shown to be involved in chemotaxis of both cell types. The receptors are responsible for the release of IL-16 from CD8$^+$ T cell. This data indicate that the $H_4$ receptor may play a role in the inflammatory response. In this paper, we applied computer aided Quantitative Structure Activity Relationship approaches such as Free-Wilson Analysis (2D) and Genetic Function Algorithm (3D) to a series of Indolylpiperazines reported in the literature$^1$ in order to develop a broadly applicable model for predicting the $H_4$–antagonistic activity.

**Free–Wilson Analysis**

The Free-Wilson analysis, proposed by Free and Wilson in 1964, is also known as additivity model and de novo approach. The basic concept of Free-Wilson analysis is the additivity principle of biological activity values. It assumes that, within a congeneric series of compounds sharing a common parent structure, the substituents make additive and constant contributions to the Biological Activity (BA) irrespective of all other structural changes in the molecule. For every compound of a congeneric series the biological activity $BA_i$ can be expressed as the sum of the biological activity contributions $\alpha_{jk}$ of the substituents (indicated by k) in each position j, and the activity contribution of the common parent structure, $\mu$. In equation, $X_{jk}$ has a value of one when the substituent $X_k$ is present in the position j, otherwise is value is zero. If the BA values are inverse molar doses, such as $1/C$, then activity-enhancing substituents have positive $\alpha_{jk}$ values, while activity-lowering substituents have negative values. The resulting regression coefficients of the indicator variables are the biological activity contributions of the corresponding structural elements. The mathematical model based on an additivity