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Quantitative Structure-Antileukemic Activity Models of Stilbenoids: A Theoretical Study

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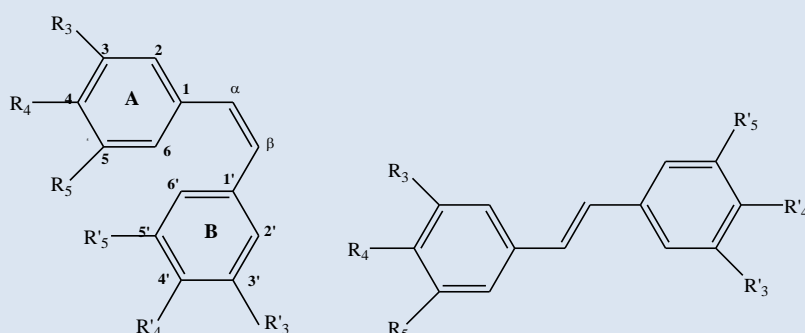
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Graphical Abstract

Figure 1. Basic molecular structure of *Z* and *E* stilbenes.

Table 1. Structures and anti-leukemic activities on HL60 cells of stilbenes [1]

STILBENOID Z (*cis*) /E (*trans*)	R_3	R_4	R_5	R'_3	R'_4	R'_5	$IC50^a$	$AC50^a$
1 E(*trans*)	OH	H	OH	H	OH	H	-0.6990	-1.6990
2 E(*trans*)	OMe	H	OMe	H	OMe	H	-0.3979	-0.6021
3 E(*trans*)	OMe	H	OMe	OMe	OMe	OMe	-1.3424	-1.6232
4 E(*trans*)	OMe	H	OMe	H	H	OMe	-1.5682	-1.8451
5 E(*trans*)	H	OH	H	H	Me	Me	-0.5441	-0.7782
6 Z(*cis*)	OMe	H	OMe	H	OMe	H	0.8239	0.6198
7 Z(*cis*)	OMe	H	OMe	OMe	OMe	OMe	-0.2553	-0.4150
8 Z(*cis*)	OMe	H	OMe	H	H	OMe	-0.4472	-0.7324

[a] Experimental data (in μM) Simoni D. *et al*.,2006 Bioorganic & Medicinal Chemistry Letters, 16, 3245-3248.

Abstract

Stilbenes are a class of plant secondary metabolites that shows a potential inhibitory effect on cellular events associated with cancer initiation, promotion and progression, as well as displays *in vitro* growth inhibition in a number of human cancer cell lines. In this report, a quantitative structure-antileukemic relationship (QSAR) of a set of stilbenes is presented. A multiple linear regression approach was adopted to determine the quantitative importance of the combined presence of some variables taken from the ChEMBL database, as well as the anti-leukemic activity that has been taken from experimental data in the technical literature of anti-proliferative effects (expressed as IC_{50}) and apoptotic inducing effects (expressed as AC_{50}) of stilbene derivatives on HL60 cells and properties of ChEMBL database. The results for the anti-leukemic activity (pIC_{50} and pAC_{50}) show positive correlations with boiling point, and numbers of Z(*cis*)-bonds and methyl groups, while negative correlations with the numbers of methoxy groups in ring B and hydroxy groups. The present results from stilbenes analysis will be useful for the anti-leukemic activity prediction of new sets of stilbenes, which will prove to be beneficial for health.

Introduction

Stilbenes are plant secondary metabolites consisting of two phenol moieties linked by a C2 bridge (Figure 1). Although the basic stilbene structure is widespread in plants, diverse species-specific substitution patterns exist. Recently, many investigations have been reported on resveratrol, a phenolic stilbene, which has been suggested as a potential chemopreventive agent based on its striking inhibitory effect on cellular events associated with cancer initiation, promotion and progression, and displayed *in vitro* growth inhibition in a number of human cancer cell lines (Jang et al., 1997; Frémont, 2000; Matsuda et al., 2001; Benlloch M., 2015; Estrela JM., 2017).

The main structural features of stilbenes have to pay attention to some structural requirements for efficient anti-leukemic activity. Even, the occurrence of substituents with positive mesomeric and inductive electronic effects increases or decreases the bioactivities of the compounds. Moreover, *Z* (*cis*) and *E* (*trans*) isomers of several analogues of stilbenes have been investigated, especially with regard to the effect of the stereochemistry of the olefinic double bond. It has been postulated and scientifically verified that the *Z* and *E* forms of stilbenes elicit different pharmacological activities (Castellano et al, 2014).

The aim of the present report is to predict the anti-leukemic activity of a set of stilbenes (Figure 1 and Table 1), based on their molecular structures and some physical and chemical properties.

Materials and Methods

A multiple linear regression approach was adopted to determine the quantitative importance of the combined presence of 22 properties or variables taken from the ChEMBL database: full molecular weight (Full mw), acd log p, rotational bonds number (rtb), heavy atoms, methoxy groups number, hydroxy groups number, methoxy groups in B-ring, Z (*cis*) bond, methyl groups number, a logp, boiling point ºC 760 mmHg, enthalpy of vaporization, ACD/logP, molar volume, polarizability, ACD log D pH 7.4, ACD/KOC pH 7.4, ACD/BCF pH 7.4, Qed weighted, Lipinski number, surface tension and density. In addition, antileukemic activity data: pIC_{50} and pAC_{50} (higher value means higher anti-leukemic activity) on HL-60 cells (Simoni D. et al, 2006).

Principal Component Analysis (PCA), linear regression correlation and multiple linear regression models were performed using SPSS (v. 21.0, IBM Corporation, USA).

Results and Discussion

The equations of multiple linear regression models to determine the quantitative importance of the combined presence of 22 properties or variables taken from the ChEMBL database with anti-proliferative effects (expressed as IC_{50}) and apoptosis inducing effects (expressed as AC_{50}) of the stilbene derivatives on HL60 cells were as follows:

pIC50 = -54.536 + [0.137 x Boiling Point] + [1.143 x Z(*cis*) bond] + [2.820 x methyl groups number] - [3.948 x methoxy groups in B-ring number] - [2.586 x hydroxy groups number]
Approximation Error Variance: 0.0495
Correlation coefficient (R): 0.999
Fisher ratio (F): 300.676
Durbin-Watson: 1.882

pAC50 = -58,198 + [0,146 x Boiling Point] + [1,181 x Z(*cis*) bond] + [3,131 x methyl groups number] - [4,174 x methoxy groups in B-ring number] - [2.993 x hydroxy groups number]
Approximation Error Variance: 0.042
Correlation coefficient (R): 1.000
Fisher ratio (F): 534.232
Durbin-Watson: 2.618

In both QSAR models, the standard error of all coefficients is lower that the corresponding value. Both linear regressions indicate that boiling point, Z(*cis*) bond and methyl groups number increase the antileukemic activity and methoxy groups in B-ring number and hydroxy groups number decrease antileukemic activity.

Figure 2 shows the clusters obtained for the stilbenes by principal components analysis (PCA). These results are according with experimental data because the stilbenes included in the same class present similar pIC_{50} and pAC_{50} values. Class 1 (compounds 2, 6, 7, 8; PC1>0, -1<PC2<1) includes the compounds with the greatest anti-leukemic activity, most characterized by Z (*cis*) bond and the presence at least 3 methoxy groups in the molecule at (6, 7, 8); class 2 (compound 5; PC1<0, PC2<<0) with high anti-leukemic activity, characterized by the presence 2 methyl groups; class 3 (compound 1, PC1<0, PC2>0) is resveratrol, with medium antileukemic activity and E (*trans*) bond; and class 4 (compounds 3, 4; PC1<<0) with low antileukemic activity and E (*trans*) bond. The variance explained by PC1 and PC2 is 74,681% (SPSS).
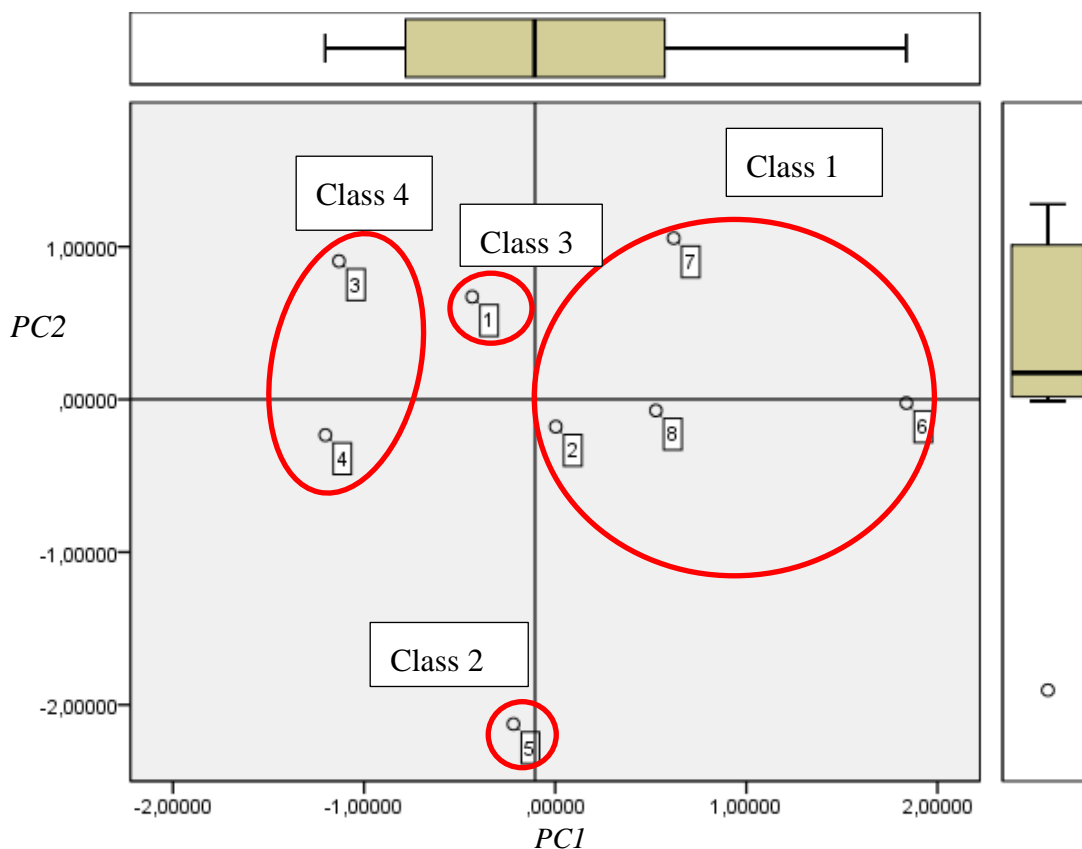

Figure 2. Stilbenes Scores Plot obtained by Principal Component Analysis and their Clusters

Figure 3 shows the loading plot of the variables that have influence in anti-proliferative effects (expressed as pIC_{50}) and apoptosis inducing effects (expressed as pAC_{50}) of stilbene derivatives on HL60 cells. The results are in concordance with the equations obtained in the multiple linear regression. Those properties most distant from point (0,0) are the most important for describing PCs, and those closest to 0,0 are less important. The PC1 (40,46% SPSS of the total variance) shows positive loading of pIC_{50}, pAC_{50}, Z(*cis*) bond, methoxyl groups number in B-ring, and boiling point, while negative loading of hydroxyl and methyl groups number. The PC2 (34,23% SPSS of the total variance) shows positive loading of Z(*cis*) bond, methoxyl groups number in B-ring and boiling point, while negative loading of methyl groups number.
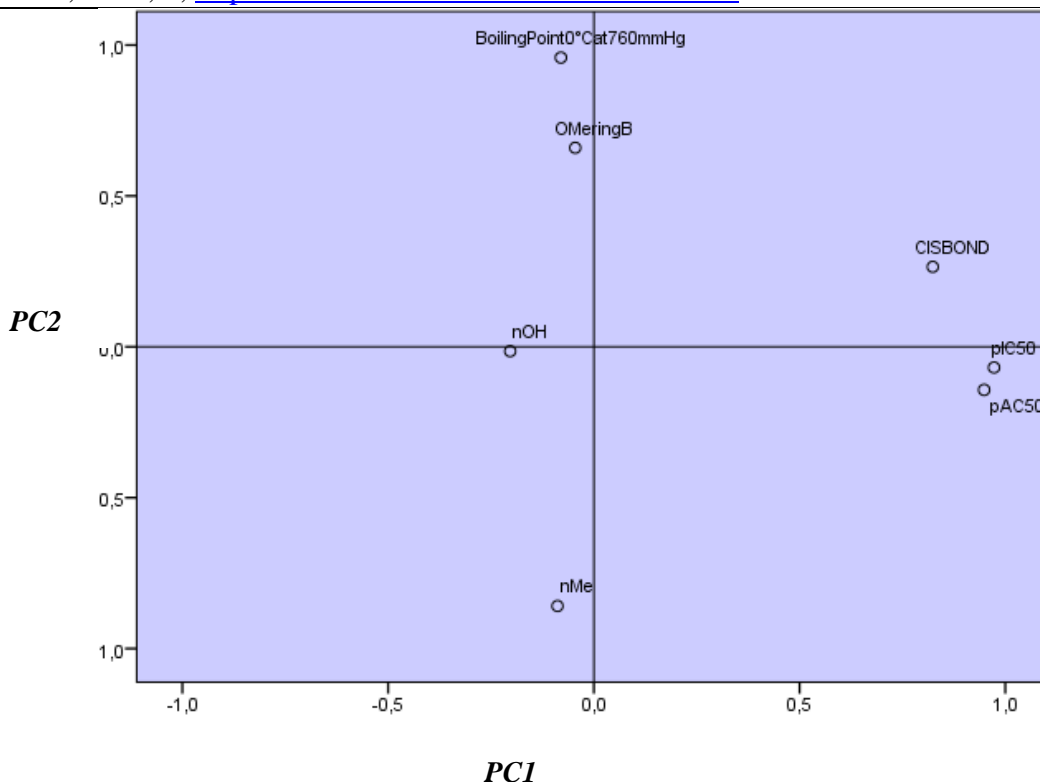
PC1
Figure 3 Loading Plot for properties of stilbenes obtained by Principal Component Analysis

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