In silico studies of sesquiterpene lactones with inhibitory activity of Nuclear Factor kappa B

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Natural products have been an important source in the discovery and development of drugs with good therapeutic activity and few adverse effects. Among them, they are plant extracts of the family Astereceae presenting antimicrobial (antibacterial and antifungal agents), anti-inflammatory and antitumoral activities. These biological activities have been associated with the presence of sesquiterpenic lactones, some of the secondary metabolites found in these plants. The antitumoral activity of sesquiterpenic lactones has been linked to the capacity of inhibiting the Nuclear Factor kappa B (NF-kB) (Merfort I. et al 2004), a transcription factor responsible for the initiation of genome transcription machine and also associated to tumorgenesis, angiogenesis and cancer metastasis, the expression of the inflammatory response and apoptosis halt.

In this work, we studied 41 sesquiterpene lactones with germanacrolide type structures, which have shown inhibition activity (IC100) for NF-kB. By means of in silico methods, we identified structural descriptors of biological activity and built a quantitative structure-activity relationship (QSAR) model with the aim of predicting putative antitumor action of sesquiterpenic lactones. The derived QSAR model equation is as follows:

$$\text{pIC}100 = -12.67 \text{GCUT\_SLOGP\_1} + 4.83 \text{Q\_VSA\_FHYD} + 0.02 \text{Q\_VSA\_PNEG} + 2.68 \text{vsurf\_CP} + 0.09 \text{vsurf\_HB7} - 0.11 \text{vsurf\_Wp5} - 10.50$$ (1)

This equation was derived using a training set of 30 molecules of the sample, displays a $R^2$ of 0.89 and an RMSE error of 0.16. Model internal validation resulted in a $R^2$ of 0.81 and an RMSE of 0.21. Finally the model was evaluated using as a test set the remaining 11 lactones of the sample, obtaining a $R^2$ of 0.71 between the calculated and measured IC100. Equation 1, overall, links the IC100 and a description of the logP (GCUT\_SLOGP\_1), the hydrophobic and polar van der Waals surface areas (Q\_VSA\_FHYD and Q\_VSA\_PNEG), the critical package (vsurf\_CP), the hydrogen donor capacity (vsurf\_HB7) and the polar superficial volume (vsurf\_Wp5).

Finally, another in silico treatment, a molecular docking, was performed to calculate the protein NF-kB -lactone interaction energy and to have a graphical image of the most significant interaction events of the ligand-protein association. The binding energy (score) was calculated using the AlphaHB score function. A 75% correlation was found between the IC100 and the docking score for the lactones with show a IC100≤50μM.