MOL2NET, International Conference Series on Multidisciplinary Sciences
http://sciforum.net/conference/mol2net-03

Modeling and prediction of anti-inflammatory activity in compounds of natural and synthetic origin

<Luis SA Torres Gómez> (luistg@ifal.uh.cu:) [a], <Enoel Hernandez Barreto> (Enoelh@uclv.edu.cu:)[b], <Yaima Garcia Guevara> (yaimag@aica.cu.cu:)[c].

[a] < Department of Pharmacy. Institute of Pharmacy and Foods. University of the Havana >

[b] < Department of Pharmacy. University Central of Las Villas >

[c] < Company Laboratories AICA>

.
.
.

In the work the MODESLAB approach is applied to the sub-structural modeling of the anti-inflammatory activity of both natural and synthetic compounds, with the purpose of calculating the spectral moments of the adjacency matrix between edges of the molecular graph with suppressed hydrogens , weighted in the main diagonal with standard dipole moments of binding to 410 active and inactive compounds. The calculated descriptors were used in the design of a training series and another one of prediction. With the training series a discriminant function was developed for the anti-inflammatory activity by means of the Multivariate Linear Regression Discriminant analysis obtaining a good total classification of 91.59%. The model was validated through the use of the prediction series, obtaining a good classification of 90.2%.

Abstract. In the work the MODESLAB approach is applied to the sub-structural modeling of the anti-inflammatory activity of both natural and synthetic compounds, with the purpose of calculating the spectral moments of the adjacency matrix between edges of the molecular graph with suppressed hydrogens , weighted in the main diagonal with standard dipole moments of binding to 410 active and inactive compounds. The calculated descriptors were used in the design of a training series and another one of prediction. With the training series a discriminant function was developed for the anti-inflammatory activity by means of the Multivariate Linear Regression Discriminant analysis obtaining a good total classification of 91.59%. The model was validated through the use of the prediction series, obtaining a good classification of 90.2%.

Introduction *(*Inflammation is a natural process, produced by the body's autoimmune system, which is mediated by different endogenous substances, such as: prostaglandins (PGs), prostacyclin (PGI2), leukotrienes (LTs) and thromboxanes (TXs), molecules of character lipid with diverse and sometimes opposing physiological actions that have the common characteristic of being synthesized from polyunsaturated fatty acids. The first attempts aimed at increasing the probability of synthesizing an active compound were based on finding correlations between the chemical structure of a series of compounds and their biological activity; thus emerging the term QSAR (Quantitative Structure-

Activity Relationship) that today is a word of current use both in the process of designing a drug and in the rationalization of a series of pharmacological properties*)*

.
.
.

Materials and Methods *(*A training series of 410 active and inactive compounds was designed. The spectral moments of each compound were obtained taking into account the molecular graphs with the dipole moment and the distance of the link; leading to the obtention of a matrix with the spectral moments from μ 0 to μ 15 for each compound. The spectral moments used were calculated with the Modeslab program. The processing of the data to create new variables was carried out with the electronic tabulator Microsoft Excel version 10.0 for Windows. Later on, the Excel's lists were worked with the software STATISTICA version 8.5 for Windows, using the linear discriminant assay for the obtention of the classification models.*)*

.
.
.

Results and Discussion *(*In this work we have had a large data of 410 compounds that include active and inactive compounds and the latter divided into 7 pharmacological groups; Among those who are antiparasitic, antihistamines, diuretics, tranquilizers, etc. This data was divided into two subseries, one containing 180 active compounds and another of 212 inactive, we must emphasize that of the total of compounds used in the training series 18 compounds were not classified by the model, it is understood unclassified compound those whose probability of classification in one group or another does not exceed 5%, once obtained the molecular descriptors are processed statistically and we obtain the discriminant equation we call the mathematical model

Class = 0.949μ0 - 0.489μ3 + 0.263μ4 - 0.038μ5 + 7.6x10-11 μ0 * μ15 -17,824

For the discrimination of active / inactive compounds studied in this paper, the model correctly classifies 91.53% of the assets and 92.00 of the inactive ones in the training series for a good overall classification of 91.59%. The percentage of false and inactive false assets in the training series is 8.00 and 8.47% respectively.

The model classifies 89.89 and 91.77% of the assets and inactive respectively, for a global classification of 90.2%. In Table # 4 and 5 the probability of subsequent classification is given according to the same criteria as for the training series, as well as the percentages of good classification. The percentage of false and inactive assets in the prediction series is: 8.23% and 11.11%, respectively.

The statistic indicates that our model is appropriate because it presents a percentage of 91.59% of good classification in the training series and 90.02% in the prediction series.

Evaluation of metabolites of medicinal plants.

Among the objectives of our work is to apply the model obtained to the prediction of metabolites of medicinal plants, in our case we have evaluated two compounds for this purpose being evaluated as anti-inflammatory, in the first case it is the ester glycoside of 24-hydroxytorméntico acid On the other hand, diosgenin was evaluated, this compound is also found in the plant in the form of a glycoside, but in this case we have only evaluated the part of the aglycone, since its ethanolic extract would be

evaluated as anti-inflammatory by other authors, giving positive this evaluation, this does not allow us to affirm that this compound has anti-inflammatory activity because in the extract not only this metabolite exists, but it constitutes a test in favor of continuing the studies of isolation, characterization and pharmacological evaluation of the same*)*

.

.

.

Conclusions *(*It was possible to design a training series and a prediction series based on the calculation of the spectral momentum of the selected compounds, using a discriminant analysis technique. And the model found was validated, evaluating the compounds of the prediction series. Metabolites of medicinal plants were evaluated, corroborating the activity of the ethanolic extract that contains one of these metabolites.

References *()*

.

1. . Guyton A, Hall J. Resistencia del organismo a la infección: Y. Leucocitos, granulocitos, el sistema macrófago-monocítico e inflamación. En: Guyton A, Hall J. Tratado de fisiología médica. McGraw-Hill interamericana, Madrid. 1996, p 477-86.

2. Esplugues J. Mediadores celulares II. Eicosanoides. En: Flores J. Farmacología humana. Ediciones Masson, SA, Barcelona. 1992, p 289-99.
3. Goodwin JS. Are prostaglandins proinflammatory, antiinflammatory, both or neither? J Rheumatol Suppl; (1991), Vol 28: p26-9.
4. Bazan N, Botting J, Vane J. New targets in inflammation. Inhibitors of COX-2 or adhesion molecules. Kluwer Academic. Dordrecht. 1996, p 1-145.

5. Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J, Perkins W, et al. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci U S A; (1994), vol 25: p12013-7.
6. Loll PJ. Stucture of prostaglandin H2 synthase-1 (COX-1) and its NSAID binding sites. En: New targets in inflamation. Inhibitors of COX-2 or adhesión molecules. Kluwer Academic. Dordrecht. 1996, p 13-21.
7. Vane JR, Botting RM. The history of anti-inflamatory drugs and their mechanism of action. En: New targets in inflamation. Inhibitors of COX-2 or adhesion molecules. Kluwer Academic. Dordrecht. 1996, p 1-12.
8. Noble, S. ; Dalfour, J.A. Meloxicam. Drug; (1996), Vol 51(3): p 426-32.

9. Barrios-Rodiles M, Keller K, Belley A, Chadee K. Nonsteroidal antiinflammatory drugs inhibit cyclooxygenase-2 enzyme activity but not mRNA. Expression in human macrophages. Biochem Biophys Res Commun; (1995), Vol 225 (3): p896-900.

.