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Relation ``structure-anticoagulant activity´´ using topologic indices

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*Received: / **Accepted**: / Published:*

The calculation methodology MODESLAB was used to modelate the anticoagulant activity of different drugs. The spectral moments of the adjacent matrix were determinated using different parameters, between the edges of the molecular graph with suppressed hydrogens, leading to the classification in active or inactives a total of 985 compounds in the main diagonal. The calculated descriptors were employed in a serie of training, as well as in a prediction one, in order to obtain and evaluate the model, respectively. A discriminant function for the anticoagulant activity was defined by the use of the training serie, leading to a good total classification of 92.29%. The external prediction one, with a total of 146 compounds, was used to validate the model, leading to a good total classification of 95.89%. The links´s contribution to the activity (understructural analysis) allowed the identification of the positive isocontribution´s zones or pharmacophere, as well as the negative isocontribution´s ones, that can functionate as groups of transport for the involved molecules; which gives us an idea of the sites that can interact with a determinated receptor, as well as those that facilitate the drug´s arriving to its site of action.

Keywords: QSAR, drugs design, anticoagulant, pharmacophere

1. Introduction

The development of information´s technologies have impacted to a widely spectrum of sciences, no being an exception the Pharmaceutical ones. The use of computational techniques during the research of new drugs remains increasing, that´s why the studies based on the relation between the chemical structure and the biologigal activity of different compounds acquire special attention. In this paper work we carried out the modelation of the anticoagulant activity of several drugs by the use of the methodology MODESLAB.

2. Results and Discussion

The model classify in a correct way the 91.29 and the 92.81% of the active and the inactive compounds of the training serie respectively, for a good total classification of 92.37%. The percentages of false actives and inactives was 7.19 and 8.71%, respectively. The false actives are inactive compounds that the model classify as actives, whereas the false inactives are active ones that the model identify as inactives. One of the most important criteria for the approval or the rejection of a discriminant model, as shows this paper work, is based on the statistics of the external prediction serie. The model was able to classify the 100 and the 94.74% of the active and the inactive ones, respectively, for a good classification total of 95.89%. The percentage of false actives and inactives in the prediction serie was 5.26 and 0%, respectively.

3. Materials and Methods

A training serie of 838 compounds was designed, with 241 in the active group and 597, in the inactive one. An external prediction serie of 146 compounds was established too, in which 32 belong to the active group and 114, to the inactive one. The spectral moments of each compound were calculated with the program MODESLAB, as consideration´s criteria for the determinations of molecular descriptors, where the links´s standard distance is of major interest. The data processing to create the new variables was carry out with the help of the electronic tabulator Microsoft Excel version 10.0 for Windows. The final step included the processing with the software STATISTICA version 8.5 for Windows, using the lineal discriminant analysis in order to obtain the classification model.

4. Analysis of the link´s contribution to the property

The evaluation of the linkages as positive or negative according to their contribution to the activity, where the total addition of these contributions represents the total contribution of the molecule, allowed us to propose the isocontribution´s sites in the molecule as posible pharmacopheres; which can be defined by the fraction of the structure that includes the linkages with positive contribution to the activity.

The underdivision of one isocontribution´s zone in synthetic groups be carry out using unconnexion´s rules, that will allow the design of an active molecule following the synthetic accessibility´s criteria. The sites with a shading appearance correspond to the active zones of the molecules, even without specify its value of contribution.

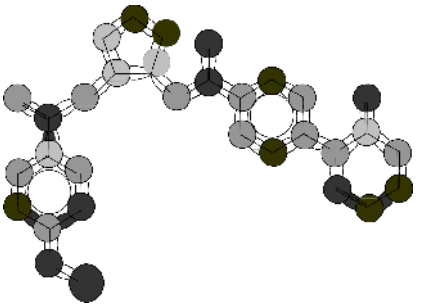

Figure 1. Chemical structure of the molecule 023A20.

The Figure 1. shows a predominance of the positive contribution´s zones in the aromatic rings and carbons´s atoms, with an electronic deficiency or excess; which suggests that the main electrostatic interaction with the repector is dipole-dipole. This idea is in correspondence with what shows the literature according to the studies about Estructure-Activity Relationship for this kind of compounds. In this field, the practice demonstrates the increase of the activity when the introduction of electroacceptors take place; but in this case we are dealing with subtitutes that extend the conugation, as well as the carbonyl case. In the other hand, from a synthetic point of view, these theories have a certain relevance due to the groups of major contribution to the activity can be introduced o

generated in specific steps of the reaction, with the objective to increase the efficiency and to reduce the collateral products.

Conclusions

A mathematical model that predicts the anticoagulant activity with a 92.29% of good classification was obtained, being validated it employing an external prediction serie with a 95.89% of good total classification. A chemical-physics interpretation of the activity, as well as of the linkage´s contribution was made.

References and Notes

1. Estrada, E., Aplication of aproximations Toss Mode. J. Chem. Inf. Comput., 1995. **35**.
2. X, J., SAR and X-ray structures of enantiopure 1,2-cis-(1R,2S)-cyclopentyldiamine and cyclohexyldiamine derivatives as inhibitors of coagulati on Factor X a. Biorganic Medicinal Chemestry., 2007.
3. Helmut Mack, Orally active thrombin inhibitors .Par t1: Optimization of the P1-moiety. Bioorg Med Chem., 2006.
4. Robert J, Structure and property based desig no ffactor Xa inhibitors Biarylpyrrolidin-2-one sin corporating basic heterocyclic motifs. BioorgMed Chem., 2007.
5. Kubinyi, H., In Hansch, C., Sammes, P. G., Taylor, J.B. and Ramdsen, C.A., Quantitative Drug Design, Pergamon. Medicinal Chemistry., 1990. **4**(5): p. 589-643.
6. Gago, F., Métodos computacionales de modelo molecular y diseño de fármacos., 2000, España: Farmaindustria. 254-256.