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[c0002]

RGD MIMETICS : BUILDING A MODEL OF RGD PEPTIDOMIMETICS WITH CoMFA AND COMPARISON WITH CATALYST

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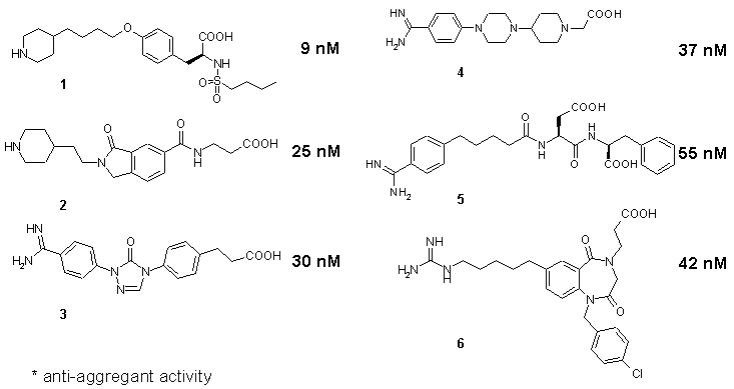
INTRODUCTION

The tripeptide sequence Arg-Gly-Asp (RGD) has been shown to inhibit the adhesive and aggregatory functions of platelets by binding to platelet receptor GP IIb/IIIa. Fibrinogen binding to GP IIb/IIIa represents the final common event that leads to platelet aggregation regardless of platelet activation and, in certain circumstances, is the primary cause of a variety of human cerebral and cardiovascular diseases[1]. The knowledge of the preferred conformation of the RGD sequence together with structure-activity relationship (SAR) analyses should lead to a better understanding of the characteristics important for high affinity binding to GP IIb/IIIa.

AIM OF THIS WORK

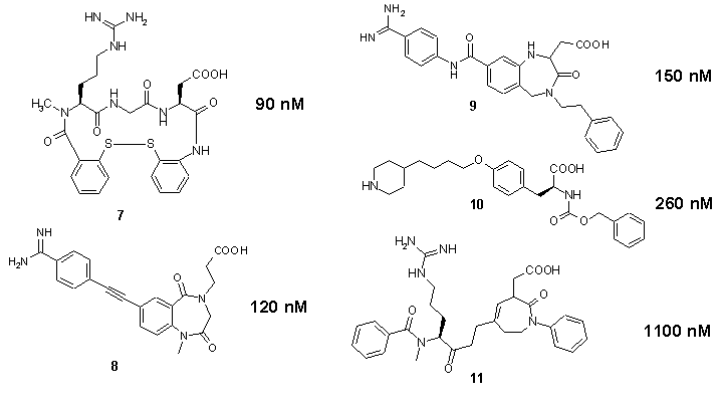
The active conformation of the flexible RGD sequence remains unknown. To overcome this problem, we performed a conformational analysis on small peptides and peptido-mimetics. Since it is now accepted that the recognized conformation is not the lowest energy conformer, the conformational analysis has considered some relatively high energy level conformers. The aim of this work is, from this conformational analysis, to propose a predictive three-dimensional model of RGD analogues, which accounts for the high affinity of these molecules for GP IIb/IIIa.

TRAINING SET (I) : IC_{50}*



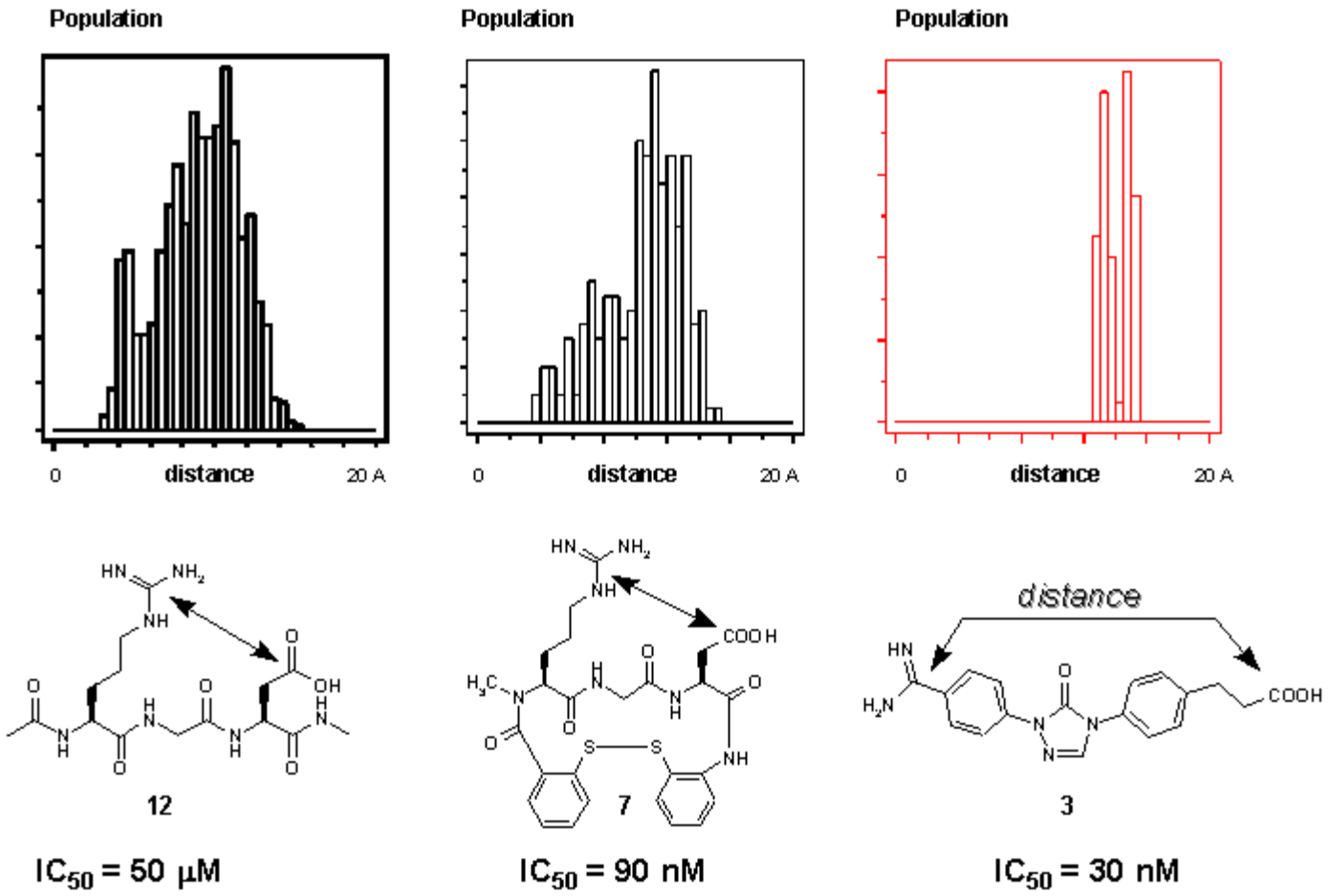
* anti-aggregant activity

TRAINING SET (II) : IC_{50}



METHOD (Conformational analysis)

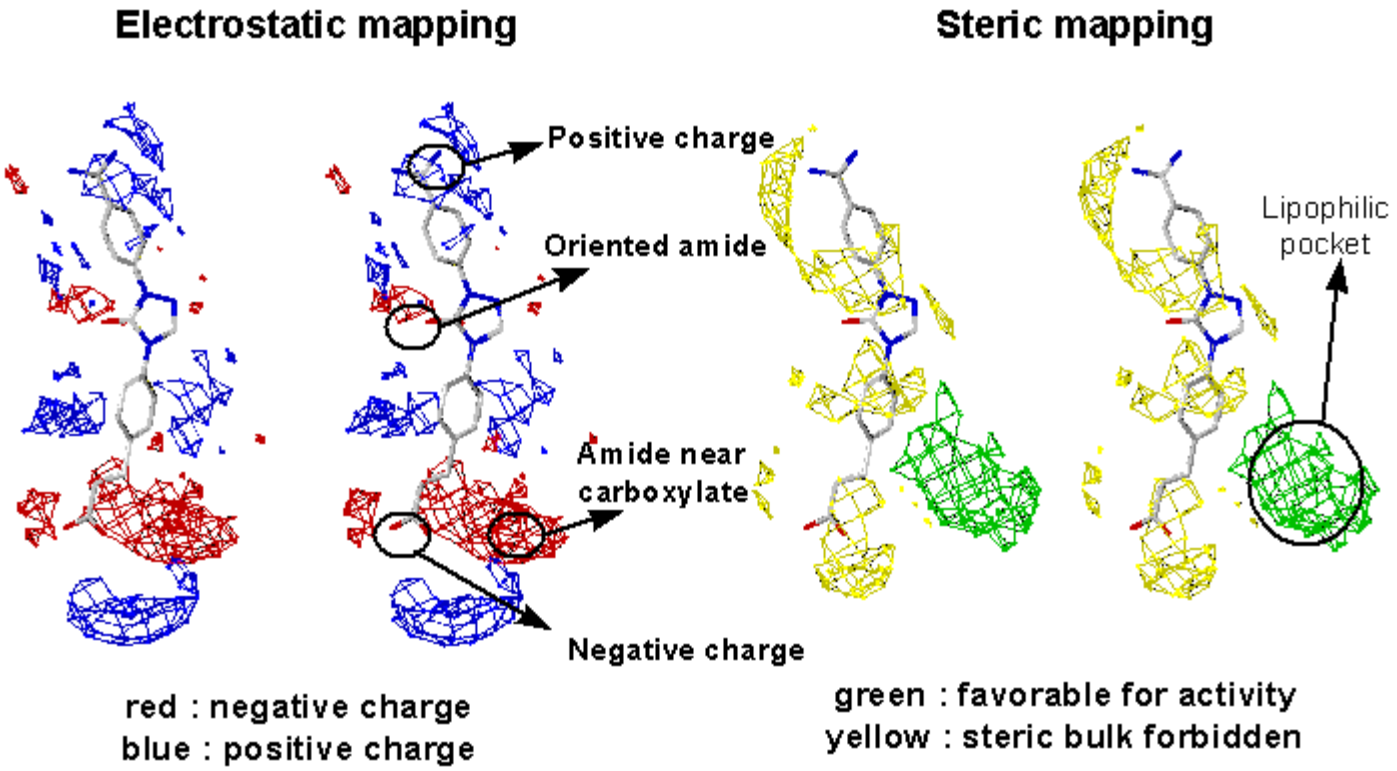
A conformational analysis was performed with the Random Search method (SYBYL[2]) with an energetic window of 30 kcal/mol[3]. We first selected 3 molecules : a linear peptide (**12**), a cyclic peptide (**7**) and a rigid nonpeptidic structure (**3**). The distance between the two charges of selected molecules was measured and used for determination of conformers populations (step 0.5Å). It appears that more a compound can frequently adopt a full extended conformation (12-14Å), more its biological activity is increased (compare **12** and **7**, **7** and **3** then **12** and **3**). On this basis, all compounds in the training set (I and II) have been treated identically and a full extended conformation for each compound was chosen for superimposition and submitted to CoMFA analysis.



CoMFA ANALYSIS

The entire CoMFA study was done using the SYBYL 6.3 program. Charges were calculated using MOPAC and AM1 method. The interaction energy matrix was calculated using the TRIPOS standard CoMFA probe (C.3, charge +1) in a box automatically determined but with a gridsize of first 20 nm (q2=0.74, r2=0.87) then 10 nm. During PLS analysis, column filtering was performed (minimum sigma 2.0). Cross-validated runs were done in order to reduce the optimum number of components for the final analysis (no cross-validation). Although q2=0.50, this model remains statistically significant. The non cross-validated results are r2=0.86, s=0.24 and F=60.4

RESULTS

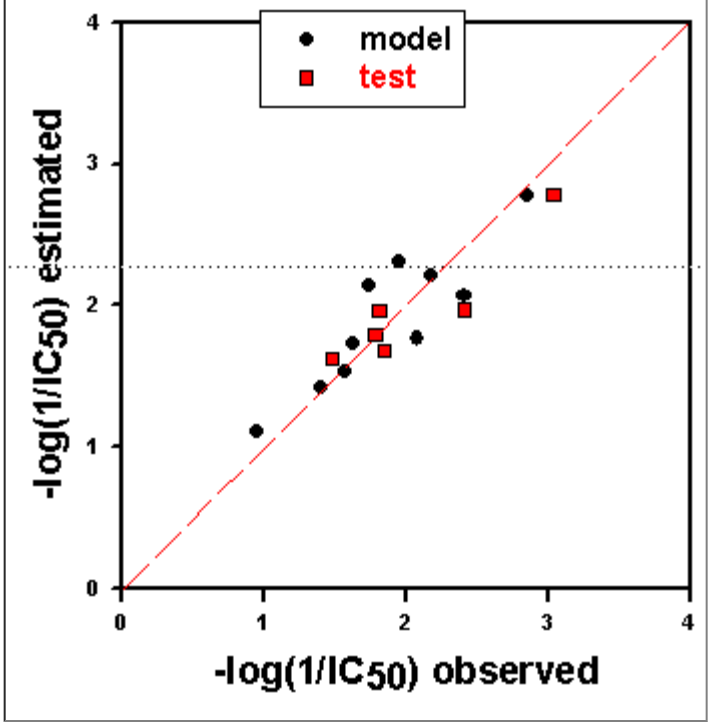


molecule 3 in the CoMFA mapping (stereo view)

VALIDATION OF THE MODEL

A set of analogs of the training set and molecules not used for the CoMFA analysis were used in order to test the predictive character of the model.

A satisfactory prediction was obtained with the test set (n) and not only for the analogs of the training set.



CATALYST PART

The range of activities was not enough for the CATALYST run, thus we have

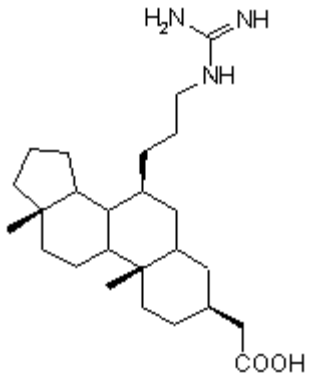
introduced a very inactive cholestane derivative (see to the right). The molecules were submitted to CATALYST hypothesis generation after conformational model were generated for all of them using 30 kcal/mol energy window above the computed minimun energy conformation.

For the hypothesis generation run, we have used the following parameters :

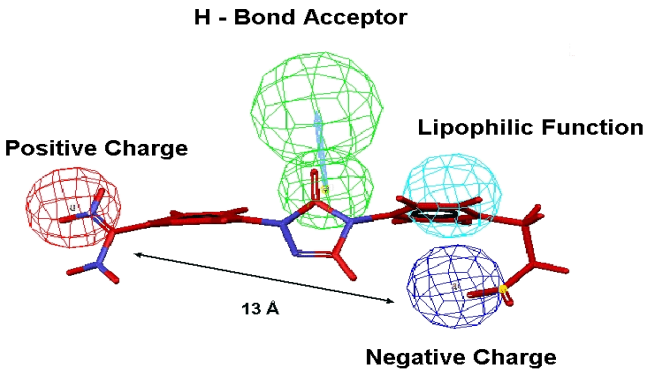
Lipohilic Function (0 to 5).
Positive Charge (1).
Negative Charge (1).
H - Bond Acceptor (0 to 5).

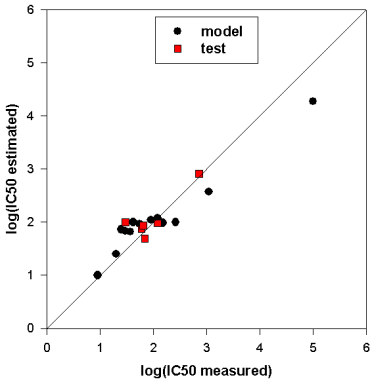
other parameters : default.

Among the 10 hypothesis generated by CATALYST, we have retained the model presenting the best correlation coefficient for the training set. This model consists of 1 positive charge (guanidinium, amidinium or secondary amine), 1 negative charge (the carboxlate), a lipophilic function located differently in comparison with CoMFA and 1 H-Bond acceptor function located in the same region than the oriented amide found with CoMFA. Finally, this model was satisfactory validated with the same test set. As previously observed with the conformational analysis, the distance between the 2 charges is 13 A.



100,000 nM





CONCLUSION

We have shown that our conformational analysis method performed on flexible and rigid molecules could be helpfull for the characterization of a first model of pharmacophore. A preliminary SAR analysis of RGD ligands highlighted two important functions for activity: a carboxylic acid and a guanidine (or a cationic equivalent). In addition, by comparing rigid and flexible molecules, it was possible to extract representative conformations. These conformations served for building an efficient CoMFA model.
In the other hand, the conformational analysis and hypothesis generation performed with CATALYST have produced a satisfactory predictive model. The geometrical description of this model is in good accordance with our conformational analysis for the CoMFA analysis.

REFERENCES

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[2] Sybyl 6.3, Tripos Associates, St Louis, Missouri, USA
[3] Nicklaus M. C., Wang S., Driscoll J. S. and Milne G. W. Bioorg. Med. Chem., 1995, 3, 411-428
[4] CATALYST, version 3.1, MSI, San Diego, CA, USA

Comments

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