International Journal of Modern Engineering Research (IJMER)
www.ijmer.com Vol.3, Issue.2, March-April. 2013 pp-1172-1175 ISSN: 2249-6645

QSAR Study for a Series of 31 Peptide-Mimetic Analogues with the Ability to Inhibit HIV-1 Protease Using Receptor Surface Analysis

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Abstract: *The quantitative structure–activity relationship analysis of a set of 31 peptide- mimetic analogues of HIV – 1 protease inhibitors was performed by receptor surface analysis. RSA is a useful tool in situations when the 3D structure of the receptor is unknown since one can build a hypothetical model of the receptor site. A receptor surface model embodies essential information about the hypothetical receptor site as a three-dimensional surface with associated properties such as hydrophobicity, partial charge, electrostatic (ELE) potential, van der Waals (VDW) potential, and hydrogen bonding propensity. The surface points that organize as triangle meshes in the construction of the RSA store these properties as associated scalar values. Receptor surface models provide compact, quantitative descriptors, which capture three-dimensional information of interaction energies in terms of steric and electrostatic fields at each surface point, which in other techniques are calculated using probe interactions at various grid points. These descriptors can be used for 3D QSAR studies.*

Key Words: *Receptor Surface Analysis, QSAR, HIV-1 Protease Inhibitors*

I. Introduction

Molecules with different substituents are generated electronically with their biological activities. All the molecules were coded with a prefix "Exa". The receptor surface model is normally generated from the most active compounds in the data set. The rationale is that the most active molecules tend to explore the best spatial and electronic interactions with the receptor, while the least active do not and tend to have unfavorable steric and electrostatic interactions. Receptor models generated using the five best active compounds Exa4, Exa6, Exa12, Exa18 and Exa33 in the training set. After the receptor surface model has been generated, all the structures in the training and test sets can be evaluated against the model. The model can be used to calculate the energy associated with the binding of a molecule in the model. It can also be used to minimize a molecule by adjusting the geometry of the structure into a "best-fit configuration" based on the constraints imposed by the receptor model. This method creates hypothetical models, called receptor surface models; those characterize the active site of macromolecule based on the construction of surfaces to represent spatial and electrostatic properties of a receptor's active site.

II. Result and Discussion

In Receptor Surface Analysis (RSA), the major steps were (1) generating conformers and energy minimization; (2) aligning molecules using the MCSG method; (3) generating the receptor model; (4) evaluating the compounds in the generated receptor model; and (5) generation of equations by the genetic function approximation method.

A receptor model was generated with the following:

- Activity data
- Soft receptor surface type
- Energies calculated using electrostatic charge complementarity

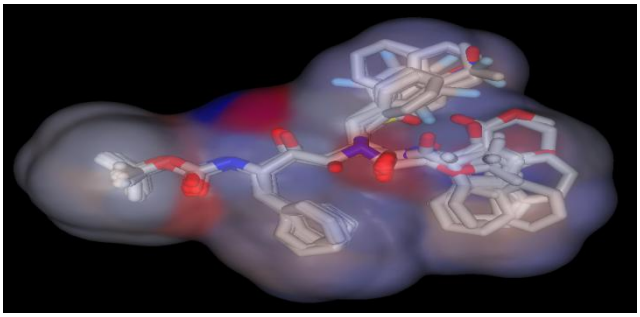
The option to minimizing molecules during evaluation was avoided. After the receptor model is generated, properties such as electrostatic potential and hydrophobicity were mapped on to the surface of the model. One property can be mapped at a time. Property maps were displayed as color regions on the receptor surface.

These properties reflect the anticipated characteristics of the receptor that is being modeled. The intensity of color reflects the magnitude of the mapped property at a particular location. Properties that can be mapped include the following:

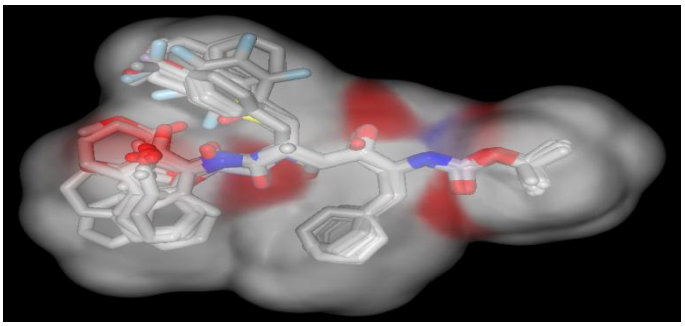
a) **Electrostatic potential:** Each surface vertex is colored according to the potential value at the vertex position. Red areas have negative electrostatic potential, blue areas have positive potential and white areas have neutral potential.
b) **Charge:** when this property is mapped, the surface color is based on the average of the charges of the template atoms closest to the receptor surface. Red areas are positively charged, blue are negatively charged and white areas neutral.
c) **Hydrogen Bonding:** The color indicates the tendency for specific areas of the surface to act as hydrogen bond donors (green) or acceptors (blue). Areas of the model with no hydrogen bonding activity are colored cyan.
d) **Hydrophobicity**: The surface is colored brown to map the hydrophobic areas of the model. Areas that are not hydrophobic relative to the scale on the panel are white.

Figure 1.1a shows the best active compounds embedded into the receptor surface model mapped with electrostatic potential; the red color represents negative energy values as favorable interaction sites, while the blue-colored regions represent positive energy values that are favorable sites for binding of the molecule on the receptor surface. Intermediate colors indicate the intensity and gray indicates neutral. Figure 1.1b shows the best active compounds embedded into the receptor surface model mapped with charge; the red areas are positively charged, the blue areas are negatively charged, and the white areas are neutral. Similarly, Figure 1.1c shows the best active compounds embedded into the receptor surface model mapped with hydrogen bonding; the blue areas act as hydrogen bond donors, the green areas act as hydrogen bond acceptors, and the pale blue do not have hydrogen bonding activity. Figure 1.1d shows the receptor surface model mapped with hydrophobicity; the brown areas are hydrophobic.

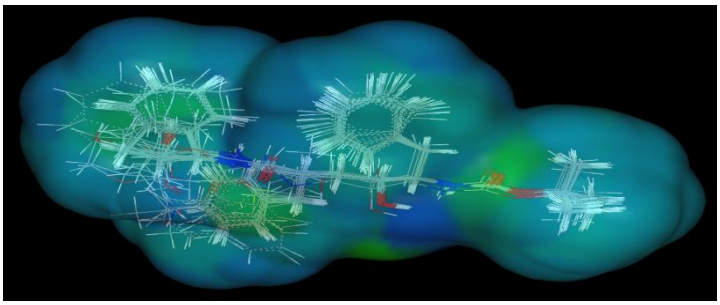
This color coding of the ligand-receptor interactions can offer a qualitative way of examining compounds, by introducing them into the virtual receptor and visually inspecting the favorable/unfavorable interactions; substituents that increase or decrease the binding affinity can be easily recognized, and one can make easily simple but accurate structure-activity estimations. Though the outcome is with statistically acceptable results for the training set, the prediction results of the test set are not equally encouraging.



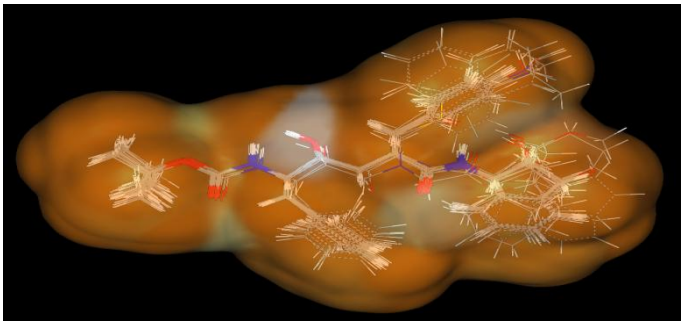
(Figure 1.1a: Electrostatic potential mapped on the receptor surface)



(Figure 1.1b: Charge mapped on the receptor surface)



(Figure 1.1c: Hydrogen bonding mapped on the receptor surface)



(Figure 1.1d: Hydrophobicity mapped on the receptor surface)

Four properties are independently mapped, generated and added them to study tables. Each study table was saved to do the QSAR model extraction. The relevant equations and their validation parameters are given here under.

Electrostatic mapping:
pIC50 = - 0.128124 - 1.33831 * "Inter VDW Energy" - 13.8893 * "VDW/693" - 27.1182 * ELE/3708"
Validation parameters are:
R−squared = 0.884
Cross validated R−squared = 0.799
PRESS = 11.89
Charge mapping:
pIC50 = 4.19565 - 11.1954 * "VDW/645" - 32.9953 * "ELE/3838" - 16.9802 * "VDW/692"
Validation parameters are:
R−squared = 0.883
Cross validated R−squared = 0.794
PRESS = 12.22
H-Bond mapping:
pIC50 = 3.76507 - 9.89141 * VDW/644" - 19.1306* "VDW/692" - 33.215 * "ELE/2131"
Validation parameters are:
R−squared = 0.874
Cross validated R−squared = 0.791
PRESS = 12.36
Hydrophobic mapping:
pIC50 = 3.75074 - 17.9708 * "VDW/692" - 12.0473 * VDW/1545" - 38.0359 * "ELE/3706"
Validation parameters are:
R−squared = 0.885
Cross validated R−squared = 0.814
PRESS = 11.03

The resultant models were of good statistical qualities having > 87 % explained variance and 79% predicted variance.

Table 1.4: Predicted activity values based on RSA

Code given	Experimental pIC50	Predicted pIC50 from RSA
Exa1	9.6	9.17
Exa3	8.11	9.25
Exa4	9.72	9.7
Exa5	9.59	9.67
Exa6	9.64	9.54
Exa7	9.22	9.64
Exa8	9.54	9.23
Exa9	9.51	9.48
Exa10	9.57	9.25
Exa11	5.53	6.34
Exa12	9.8	9.27
Exa13	7.56	6.73
Exa14	9.14	8.81
Exa15	8.27	8.89
Exa16	9.28	8.66
Exa17	9.6	9.75
Exa18	9.77	9.94
Exa19	6.94	6.75
Exa20	8.02	8.4
Exa21	7.47	8.07
Exa22	6.16	6.77
Exa23	6.79	6.57
Exa24	7.18	8.93
Exa25	6.67	9.19
Exa30	4.52	4.24
Exa31	6.89	6.45
Exa32	6.84	6.69
Exa33	10	10.22
Exa34	7.41	6.71
Exa49	5.33	5.4
Exa50	5.86	6.34

III. Conclusion

The descriptors VDW/693, ELE/3708, ELE/3838, VDW/692, VDW/644, VDW/692, ELE/2131, VDW/692, VDW/1545, ELE/3706, etc. are contributing at the grid point numbers in the space. The location and magnitude of a descriptor can be used as a guideline to improve the activity of molecules.

IV. Acknowledgement

I would sincerely thank Dr. M. Kishore Kumar, bio-Campus, Hyderabad for his guidance and invaluable technical assistance. My grateful acknowledgments are due to the management of bio-Campus, Hyderabad, for providing excellent working atmosphere with modern equipment in drug discovery and design during my stay at their campus.

References

[1] David E. Clark, David R. Westhead Journal of Computer-Aided Molecular Design 1996, 10 (4), 337-358-
[2] Hansch, C.; Leo, A.; Hoekman, D. (1995) Exploring QSAR. Hydrophobic, Electronic and Steric Constants; American Chemical Society: Washington, DC.
[3] Hahn, M. (1995) Receptor Surface Models. 1. Definition and Construction. J. Med. Chem., 38, 2080-2090.
[4] Franke, R. Theoretical Drug Design Methods; Elsevier: Amsterdam, 1984.
[5] Franke, R.; Gruska, A. (1995) In Chemo metric Methods in Molecular Design; van de Waterbeemd, H., Ed.; VCH: Weinheim, Vol. 2, pp 113-163.
[6] Kamal Azzaoui, Maria J. Diaz-Perez, Maria Zannis-Hadjoupoulos, Gerry B. Price, and Irving W. WainerJournal of Medicinal Chemistry **1998**, 41 (9), 1392-1398
[7] Sung-Sau So and Martin KarplusJournal of Medicinal Chemistry 1997, 40 (26), 4347-4359
[8] Rohrbaugh, R.H., Jurs, P.C., (1987) "Descriptions of Molecular Shape Applied in Studies of Structure/Activity and Structure/Property Relationships", Analytica Chimica Acta, 199, 99-109.
[9] Holloway, M. K., J. M. Wai, et al. (1995). "A priori prediction of activity for HIV-1 protease inhibitors employing energy minimization in the active site." J Med Chem 38(2): 305-17.
[10] Rogers, D.; Hopfinger, A. (1994) J. Application of genetic function approximation to quantitative structure-activity relationships and quantitative structure-property relationships. J. Chem. Inf. Comput. Sci., 34, 854-866.
[11] Chong Hak Chae, Sung-Eun Yoo, and Whanchul ShinJournal of Chemical Information and Computer Sciences 2004, 44 (5), 1774-1787
[12] Antonio Macchiarulo, Gabriele Costantino, Mirco Meniconi, Karin Pleban, Gerhard Ecker, Daniele Bellocchi, and Roberto PellicciariJournal of Chemical Information and Computer Sciences 2004, 44 (5), 1829-1839
[13] Jaroslaw Polanski, Rafal Gieleciak, Tomasz Magdziarz, and Andrzej BakJournal of Chemical Information and Computer Sciences 2004, 44 (4), 1423-1435
[14] http://www.ccdc.cam.ac.uk/products/csd/
[15] http://www.rcsb.org/pdb/home/home.do
[16] C. Pérez, M. Pastor, A.R. Ortiz, F. Gago, Comparative binding energy analysis of HIV-1 protease inhibitors: incorporation of solvent effects and validation as a powerful tool in receptor-based drug design, J. Med. Chem. 41 (1998) 836–852.
[17] A. Wlodawer, J. Vondrasek, Inhibitors of HIV-1 protease: a major success of structure-assisted drug design, Annu. Rev. Biophys.Biomol. Struct. 27 (1998) 249–284.
[18] A. Gavezzotti, Molecular packing and correlations between molecular and crystal properties, in: H.-B. Bürgi, J.D. Dunitz (Eds.), Structure Correlation, vol. 2, VCH, Weinheim, 1994, pp. 509–542.
[19] C. Flexner, HIV-1 protease inhibitors, New Engl. J. Med. 338 (1998) 1281–1292.
[20] K.R. Beebe, R.J. Pell, M.B. Seasholtz, Chemo metrics: A Practical Guide, Wiley, New York, 1998.
[21] Pirouette, Version 2.7., Infometrix Inc., Seattle, WA, 2000.
[22] M. Sakurai, S. Higashida, M. Sugano, H. Handa, T. Komai, R. Yagi, T. Nishigaku, Y. Yabe, Studies of human immunodeficiency virus type 1 (HIV-1) protease inhibitors. III. Structure–activity relationship of HIV-1 protease inhibitors containing cyclohexylalany lalanine hydroxyethane dipeptide isostere, Chem. Pharm. Bull. 42 (1994) 534–540.