

Optimization of Carbocyclic Analogues to a Pharmaceutical Enzyme Target via Discovery Studio™

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Abstract:

The following teaching biochemistry laboratory experiment introduces students to principles of structure-based drug design and the important role that molecular modeling plays in optimizing drug leads. The discovery and development of the potent, orally bioavailable influenza antiviral oseltamivir (Tamiflu) is highlighted. The user-friendly graphical interface of the Discovery Studio molecular modeling software provides an excellent environment to introduce students to the techniques of molecular minimization and calculation of relative enzyme/inhibitor interaction energies. A strong correlation between the experimentally determined inhibition constant values of various oseltamivir carbocyclic analogues and calculated relative interaction energies is obtained.

Presented Topics:

- Molecular mechanics
- Force field
 - $E = E_B + E_A + E_T + E_I + E_{VDW} + E_Q + E_{HB}$ (Dreiding) [1]
 - Energy Minimizations
 - Local potential energy minimum and global minimum

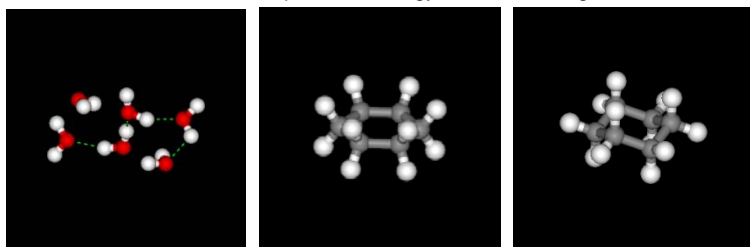


Figure 1 Left - Minimized water system depicting optimized hydrogen bonds. Middle - Local cyclohexane minimized structure - 34 kcal/mole. Right - Global cyclohexane minimized structure - 11 kcal/mole.

Determination of Relative Interaction Energies of Inhibitors to a Receptor Enzyme

- Interaction Energy
 - $\Delta E_i = E[\text{Enz}:I] - E[I] - E[\text{Enz}]$
- Relative Interaction Energy
 - $\Delta\Delta E_i = \Delta E_{i,\text{analogue}} - \Delta E_{i,\text{reference}}$

Determination of Relative Interaction Energies of Various Carbocyclic Inhibitor Analogues to Neuraminidase of Influenza Virus and Drug Lead Optimization

- Neuraminidase subtype 1/oseltamivir carboxylate complex crystal structure
 - 2HU4.pdb [2]
- Gilead Sciences
 - Structure activity relationship [3]
- Academia Sinica
 - Tamiphosphor development [4]
- Importance of Correlation Between Experimental and Theoretical Results
 - Similar established method [5]

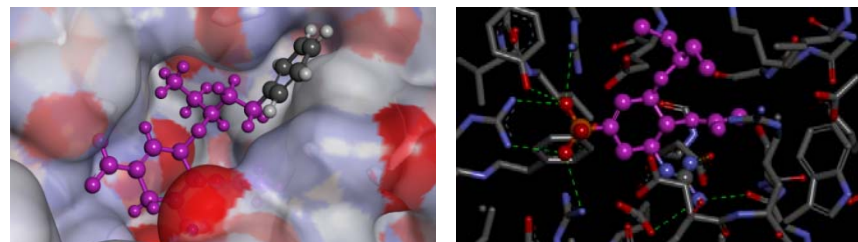


Figure 2 Left - Compound 17 [3] minimized within the active site of influenza neuraminidase type 1. Right - Compound 13b [4] minimized within the active site of influenza neuraminidase type 1.

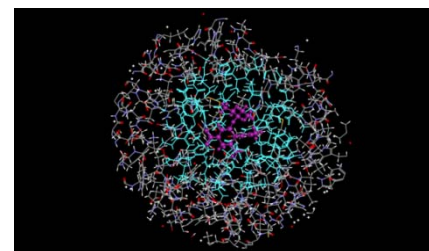


Figure 2 Left - "Reduced" oseltamivir carboxylate/neuraminidase active site. The active site system includes the inhibitor (pink) and all atoms (light blue) of the neuraminidase structure within 8 angstroms of the inhibitor. The remaining atoms (element colors) are within 16 angstroms of the inhibitor.

| Compound | Ki (nM) [4] | $\Delta\Delta E_i$ (kcal/mole) |
|------------------------------|-------------|--------------------------------|
| Oseltamivir carboxylate (OC) | 2.90 | 0 |
| 13a (Guanidine-OC) | 2.02 | -2.23 |
| Tamiphosphor | 0.15 | -3.39 |
| 13b | 0.06 | -5.16 |
| Combined 13b and 17 | | -7.78 |
| Drug lead optimization | | -8.40 |

References

- [1] Mayo S, Olafson B, Goddard W, J. of Phys. Chem. 94, 8897 - 8909 (1990)
 [2] Russell et al., Nature 443, 45-49 (2006)
 [3] Lew et al., Curr. Med. Chem. 7, 663 - 672 (2000)

- [4] Shie J J et al., JACS 129, 11892-11893 (2007)
 [5] Nair et al., J. Mol. Graph. Modelling 21, 171-179 (2002)