Docking studies of pyrrole derivatives using Hex

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ABSTRACT

N-substituted pyrrole derivatives block HIV fusion. Docking used for virtual screening of database and for the prediction of the strongest binders based on various scoring functions. Docking studies were carried out on different pyrrole derivatives for better anti-HIV-1 activity which is important for the development of a new class of inhibitors. Protein-ligand interaction plays an important role in structural based drugs design. In our research we have selected different receptor which shows anti-HIV-1 activity. The receptors were docked with different pyrrole derivatives and the energy value obtained. Our study reveals that the highest energy values observed for all the three ligands are with 3MNW: for 2-Amino-1-(4-Iodo-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester energy value is -265.9, for 2-Amino-1-(4-Fluoro-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester energy value is -228.23 and for 2-Amino-1-(4-Methoxy-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester energy value is -227.13. From this we can say that Iodo pyrrole derivative shows high interaction energy compared to other Fluoro and methyl derivatives. By synthesizing few more analogous, we can further improve the interaction energy values and hence better analogous derivatives can be predicted.

Keywords: N-substituted pyrrole, anti-HIV-1 activity, Protein-ligand interaction, interaction energy, Hex.

1. Introduction

According to the estimate of UNAIDS, about 33.2 million people worldwide are living with HIV, and more than 25 million patients have died of AIDS (www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007/). Thus far, 28 anti-HIV drugs have been licensed by the United States Food and Drug Administration (FDA) (http://www.hivandhepatitis.com/hiv_and_aids/hiv_treat.html). N-substituted Pyrroles designated NB-2 and NB-64 inhibited HIV-1 replication at a low micro molar range (Shibo, Jiang et al., 2004). The fusion and entry of HIV into susceptible cells are mediated by its envelope glycoproteins gp41 and gp120.12 Gp120 directs the virus to the appropriate target cell by binding to the rHuman T-cell receptor (CD4) and chemokine co-receptor CCR4 (also called fusin) or CCR5 (chemokine C–C motif receptor 5) (Chan D et al., 1998, Wyatt R et al., 1998). Pyrrole and its derivatives show different biological activities such as antibacterial (Demirayak, S et al., 1999), antitumor (Halazy, S. & Magnus, P., 1984), analgesics (B.Li et al., 1985), antitubercular (Bijev, A. 2006, Sbardella, G. et al., 2004) anti-inflammatory and antiallergic (Briken, C et al., 1986). Synthesized pyrrole have been used in the pharmaceutical industry and are precursors in the synthesis of porphyrins and other macro
cycles which are finding increasing use in the medicinal and material science (Bonnet, R. 1995, Grive, M.B et al., 1994). Computational Biology and bioinformatics are useful for the drugs recovery process which reduces the cost of drugs. Rational Drug Design is the inventive process of finding new medications based on the knowledge of the biological target. (Madsen, Ulf et al., 2002). Docking of the drug molecule with the receptor is one of the methods to identify novel compounds. The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor (Choi YL et al. 2008).

2. Methodology

Computer-Aided Drug Design (CADD) is a specialized discipline for the study of simulation of ligand-receptor interactions and is strongly dependent on bioinformatics tools, applications and databases. The structure of Pyroles receptors were referred from different journals and retrieved from PDB (www.pdb.org/pdb). Three analogous N-substituted pyrrole derivatives which have been synthesized by us and three dimensional structures of all these derivatives have been worked out. The corresponding CIF files of these derivatives have been converted into PDB file using OBGUI software (Morley, C. 2006). These PDB structures are used for the docking studies using Hex software (Ritchie, D.W. 2003). The receptor proved to be the best inhibitor of the ligand when ligand-receptor dock each other well.

The parameters used for the docking process were

1. Correlation type – Shape only
2. FFT Mode - 3D fast lite
3. Grid Dimension - 0.6
4. Receptor range – 180
5. Ligand range – 180
6. Twist range – 360
7. Distance Range – 40

The selected pyrrole derivatives were docked with the receptor using the above parameters.

3. Results and discussion

Docking results between the Iodo derivative of pyrrole (2-Amino-1-(4-Iodo-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester) (Barot, R.A, 2009) and few selected receptors are tabulated in (Table 1). The structure of ligand is shown in (Fig 1). From the table it can be concluded that the ligand-receptor fitting (Fig 2) is best with 3MNW (energy value -265.9).

<table>
<thead>
<tr>
<th>Table 1: Docking results of Compound A and different receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule A</td>
</tr>
<tr>
<td>E-Value</td>
</tr>
</tbody>
</table>
The analog of molecule A in which Iodine is replaced by the Fluorine (Fig 3) was synthesized in the lab and the docking results between the drug (molecule B) [2-Amino-1-(4-Fluoro-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester](Jotaniya, C.G, 2009) and
the selected receptors are tabulated in (Table 2). The results show that 3MNW is the best receptor for this derivative as the energy is -265.9.

**Table 2: Docking results of molecule B and different receptors**

<table>
<thead>
<tr>
<th>2-Amino-1-(4-Fluoro-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester (Molecule B)</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1DFB</td>
<td>2EBO</td>
</tr>
<tr>
<td>E-Value</td>
<td>-214.4</td>
</tr>
</tbody>
</table>

The another analog of molecule A in which Iodine is replaced by the Methyl moiety (Modh, R.D, 2010) (Fig 4) was synthesized in the lab and the docking results between the drug (molecule B) and selected receptors are tabulated in (Table 3).

**Figure 3: Structure of Molecule C**

The results shows that **3MNW** is the best receptor for this derivative too as the energy is **-227.13**

**Table 3: Docking results of Molecule C and different receptors**

<table>
<thead>
<tr>
<th>2-Amino-1-(4-Methoxy-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester (Molecule C)</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1DFB</td>
<td>2EBO</td>
</tr>
<tr>
<td>E-Value</td>
<td>-176.7</td>
</tr>
</tbody>
</table>
We can conclude that the molecules A, B, C having highest interaction energy with 3MNW receptors. Out of these three Iodo pyrrole derivative (molecule A) showed the high energy values (-265.9), which means that it was more compatible with receptor compare to other analogous.

4. References


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22. Shibo, Jiang, Hong Lu, Shuwen Liu, Qian Zhao, Yuxian He & Debnath, A.K., (2004), N-Substituted Pyrrole Derivatives as Novel Human Immunodeficiency Virus Type 1 Entry Inhibitors That Interfere with the gp41 Six-Helix Bundle Formation and Block Virus Fusion, Anti microbial agents and chemotherapy, 48 (11), pp 4349-4359.


