In Silico Design of New Drugs for Myeloid Leukemia Treatment

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1. Introduction
2. Materials and Methods
3. Results and Discussion
4. Conclusions
5. Acknowledgments
In this work we use *in silico* tools like *de novo* drug design, molecular docking and absorption, distribution, metabolism and excretion (ADME) studies in order to develop new inhibitors for tyrosine-kinase protein (including its mutate forms) involved in myeloid leukemia disease. This disease is the first cancer directly associated with a genetic abnormality and is associated with hematopoietic stem cells that are manifested primarily with expansion myelopoiesis. Starting from a family of fragment and seeds from known reference drugs, a set of more than 6k molecules were generated. This first set was filtered using the Tanimoto similarity coefficient as criterion. The second set of more dissimilar molecules were then used in the docking and ADME studies. As a result, we obtain a group of molecule that inhibit the tyrosine-kinase family and have ADME properties better than the reference drugs used in the treatment of myeloid leukemia.
Materials and Methods

Protein
1. Tyrosine-kinase in its wild form (1OPJ)¹
2. Mutated tyrosine-kinase²

Softwares
1. Schrodinger Suite³
2. Maestro interface⁴
3. LigBuilder⁵,⁶

Molecules
1. Grown/Linked from fragment database⁶
2. Reference drugs: imatinib, dasatinib, nilotinib and ponatinib

Steps
1. Prepare the protein
2. Grown/link new molecules (library no. 1)
3. Filter library no. 1 (library no. 2)
4. Calculate ADME properties
5. Dock (rigidly) library no. 2 and reference drugs
6. Dock (flexibly) best molecules from step 5 and reference drugs
To validate the structural diversity of the generated library we calculated a 2D linear hashed fingerprint with a 64-bit address space. Then, we used the Tanimoto metric to compute the similarity among all the molecules (if the Tanimoto coefficient of two structures is greater than 0.85, the structures are considered similar, and descarted).
Results and Discussion

Use of Lipinski’s rule of five\(^7\): widely used descriptor to study the drugability of molecules. It predicts that a molecule will have poor absorption when:
- MW > 500Da
- QPlogPo/w > 5
- HBDonor > 5
- HBAcceptor > 10

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>QPlogPo/w</th>
<th>HBDonor*</th>
<th>HBAcceptor*</th>
<th>QPlogHERG</th>
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</thead>
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<td>Imatinib</td>
<td>493.610</td>
<td>3.476</td>
<td>2</td>
<td>10.00</td>
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<td>Dasatinib</td>
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<td>Nilotinib</td>
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<tr>
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<td>781</td>
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- As they are average values, they can be non-integers.
  Red values = bad values!

MW: molecular weight
QPlogPo/w: octanol/water partition coefficient
HBDonor: number of hydrogen bonds that would be donated by the solute to water molecules
HBAcceptor: estimated number of hydrogen bonds that would be accepted by the solute from water molecules
QPlogHERG: simulate the blockage of human ether-a-go-go hERG K+ channels (cardiac side effects).
Results and Discussion

Absorption, Distribution, Metabolism and Excretion
## Results and Discussion

### Docking results: scores

**Table 1.1 Docking score (Gscore*) for the best molecules and for the references drugs (the lower the better).**

<table>
<thead>
<tr>
<th></th>
<th>Molecule</th>
<th>1OPJ</th>
<th>680</th>
<th>632</th>
<th>681</th>
<th>781</th>
<th>723</th>
<th>721</th>
<th>670</th>
<th>700</th>
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<tbody>
<tr>
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<td>Reference</td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>Nilotinib</td>
<td>Ponatinib</td>
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<tr>
<td>T315I</td>
<td>Molecule</td>
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<td>687</td>
<td>715</td>
<td>688</td>
<td>711</td>
<td>703</td>
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<td>T315A</td>
<td>Molecule</td>
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<td>688</td>
<td>711</td>
<td>721</td>
<td>687</td>
<td>715</td>
<td>751</td>
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<tr>
<td></td>
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<td>Dasatinib</td>
<td>Nilotinib</td>
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* In kcal/mol
## Results and Discussion

### Docking results: scores

Table 1.2 Docking score (Gscore*) for the best molecules and for the references drugs.

<table>
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<tr>
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<th>Molecule</th>
<th>723</th>
<th>681</th>
<th>559</th>
<th>558</th>
<th>781</th>
<th>700</th>
<th>646</th>
<th>647</th>
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<td>Imatinib</td>
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<td>Ponatinib</td>
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<td>Reference</td>
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<td>Nilotinib</td>
<td>Ponatinib</td>
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<td></td>
<td>Reference</td>
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<td>Dasatinib</td>
<td>Nilotinib</td>
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<td>Dasatinib</td>
<td>Nilotinib</td>
<td>Ponatinib</td>
</tr>
</tbody>
</table>

* In kcal/mol
## Docking results: interaction energies

<table>
<thead>
<tr>
<th>Complex</th>
<th>HBondE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>LipoE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ElectE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HBond&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Good&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Bad&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ugly&lt;sup&gt;b&lt;/sup&gt;</th>
<th>π-π&lt;sup&gt;b&lt;/sup&gt;</th>
<th>π-cation</th>
<th>HBondD&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1OPJ&lt;sup&gt;+&lt;/sup&gt;680</td>
<td>−3.226</td>
<td>−7.705</td>
<td>−1.061</td>
<td>6</td>
<td>486</td>
<td>9</td>
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<td>1</td>
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<tr>
<td>1OPJ+Imatinib</td>
<td>−2.499</td>
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<td>−1.550</td>
<td>4</td>
<td>516</td>
<td>12</td>
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<td>1</td>
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<td>1.711, 1.895, 1.934, 2.005</td>
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<tr>
<td>T315I&lt;sup&gt;+&lt;/sup&gt;781</td>
<td>−3.407</td>
<td>−7.540</td>
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<tr>
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<td>−2.312</td>
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<td>0</td>
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<tr>
<td>E355G&lt;sup&gt;+&lt;/sup&gt;781</td>
<td>−4.282</td>
<td>−7.545</td>
<td>−1.151</td>
<td>5</td>
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<td>1.648, 1.948, 1.970</td>
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</table>

<sup>a</sup> In kcal/mol.

<sup>b</sup> Number of contacts.

<sup>c</sup> H-Bond distances, in Å.
Results and Discussion

Docking: 2D interactions

1OPJ+680

1OPJ+Imatinib
Results and Discussion

Docking: 2D interactions

T315I

T315I+781

T315I+Imatinib
Docking: 2D interactions

M244V+723

M244V+Nilotinib

Results and Discussion

Docking: 2D interactions
M244V
Results and Discussion

Docking: 2D interactions

E355G+781

E355G+Nilotinib
Results and Discussion

Docking: 2D interactions
H396A

H396A+781

H396A+Nilotinib

- Charged (negative)
- Charged (positive)
- Polar
- Hydrophobic
- Glycine
- Metal
- Water
- Hydration site
- Displaced hydration site
- π-π stacking
- π-cation
- H-bond (backbone)
- H-bond (side chain)
- Metal coordination
- Salt Bridge
- Solvent exposure
The myeloid leukemia is a fatal disease, so it is of great importance to keep the patients in chronic phase where they stay asymptomatic. The fragment based drug design method used in this work turns to be a good alternative to create drugs that can control this neoplasm. Based on the calculated GScore, the *de novo* designed molecules have better inhibitor capacity than the tyrosine-kinase inhibitors most used in the market. These molecules shown strong potential to become drugs capable to inhibit all mutations, mainly the T315I mutation, now the leading cause of deaths due to the difficulty of inhibitors to control it.
Acknowledgments

http://www.unifal-mg.edu.br

http://www.fapemig.br/

http://www.cnpq.br/

http://www.capes.gov.br/
References


