In Silico Design of New Drugs for Myeloid Leukemia Treatment

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Introduction

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-kinase[2]

Softwares

1. Schrodinger Suite[3]
2. Maestro interface[4]
3. LigBuilder[5,6]

Molecules

1. Grown/Linked from fragment database[6]
2. Reference drugs: imatinib, dasatinib, nilotinib and ponatinib

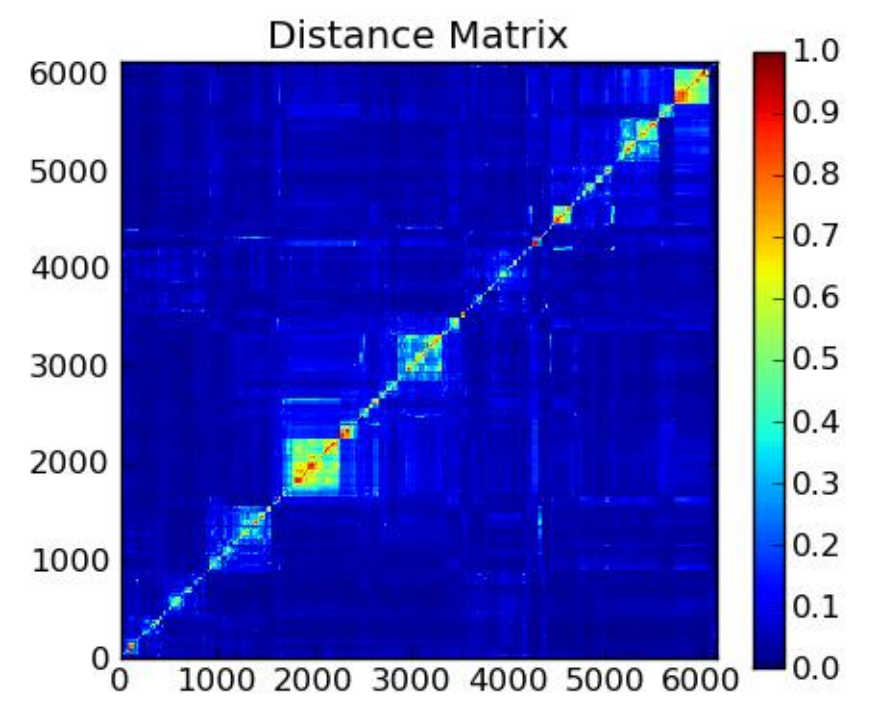
Steps

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

Results and Discussion

Filtering

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

Absorption, Distribution, Metabolism and Excretion

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

Compound	MW	QPlogPo/w	HBDonor*	HBAcceptor*	QPlogHERG
Imatinib	493.610	3.476	2	10.00	-9.280
Dasatinib	488.006	2.509	3	10.00	-6.672
Nilotinib	529.523	5.870	2	8.00	-8.246
Ponatinib	532.567	4.602	1	9.50	-9.243
680	487.511	1.856	5	10.00	-6.307
723	430.502	4.471	3	6.25	-8.392
781	459.498	4.960	3	6.75	-5.837

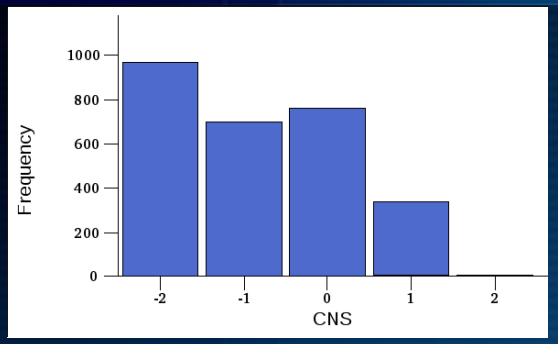
- As they are average values, they can be non-integers.

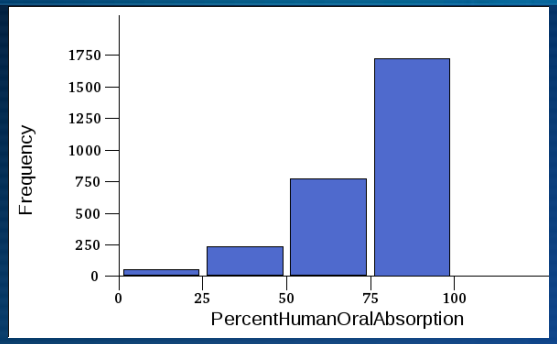
Red values = bad values!

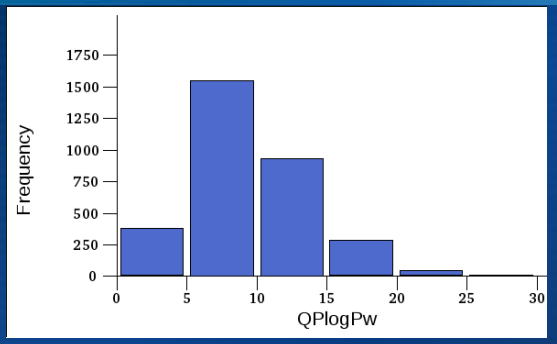
MW: molecular weight
QPlogPo/w: octanol/water partition coefficient
HBDonor: number of hydrogen bonds that would be donated by the solute to water molecules
HBAcceptor: estimated number of hydrogen bonds that would be accepted by the solute from water molecules
QPlogHERG: simulate the blockage of human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

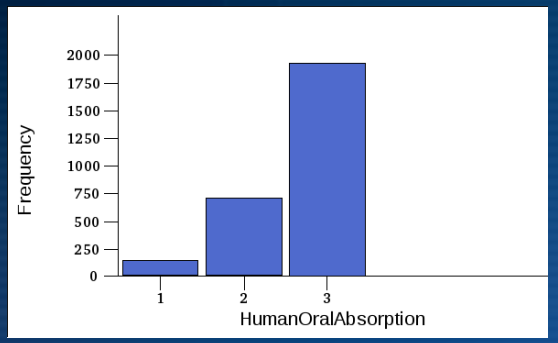
Results and Discussion

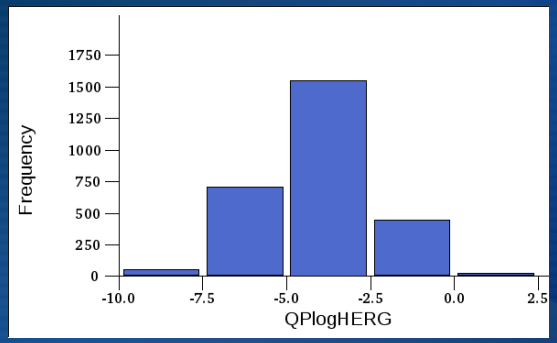
Absorption, Distribution, Metabolism and Excretion

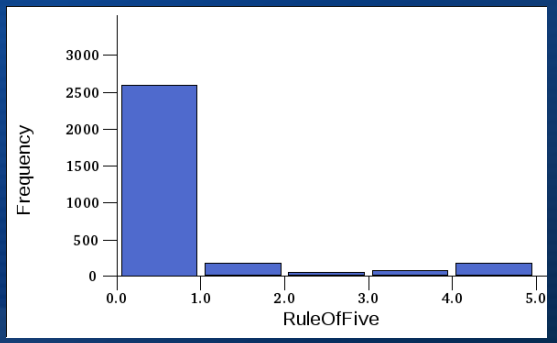


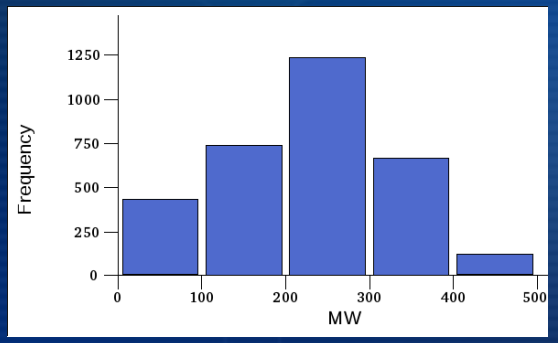


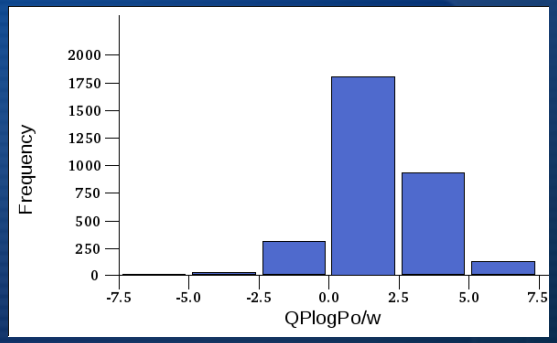


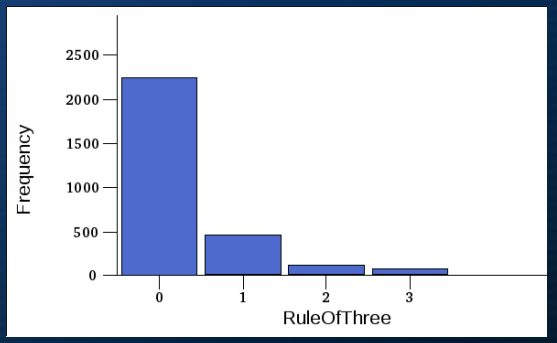












Results and Discussion

Docking results: scores

Table 1.1 Docking score (Gscore*) for the best molecules and for the references drugs (the lower the better).									
1OPJ	Molecule	**680**	**632**	**681**	**781**	**723**	**721**	**670**	**700**
	GScore	-15.34	-15.332	-15.148	-15.132	-14.601	-14.445	-14.394	-14.369
	Reference	Imatinib	Dasatinib	Nilotinib	Ponatinib				
	GScore	-13.955	-9.079	-13.631	-12.961				
T315I	Molecule	**781**	**687**	**715**	**688**	**711**	**703**	**674**	**701**
	GScore	-13.571	-13.419	-13.419	-13.402	-13.402	-12.96	-12.943	-12.916
	Reference	Imatinib	Dasatinib	Nilotinib	Ponatinib				
	GScore	-13.313	-7.223	-4.892	-11.922				
T315A	Molecule	**781**	**688**	**711**	**721**	**687**	**715**	**751**	**559**
	GScore	-14.16	-14.093	-14.093	-14.038	-13.92	-13.92	-13.884	-13.764
	Reference	Imatinib	Dasatinib	Nilotinib	Ponatinib				
	GScore	-13.054	-9.901	-13.487	-13.086				

* In kcal/mol

Results and Discussion

Docking results: scores

Table 1.2 Docking score (Gscore*) for the best molecules and for the references drugs.									
M244V	Molecule	**723**	**681**	**559**	**558**	**781**	**700**	**646**	**647**
	GScore	-14.954	-14.804	-14.47	-14.442	-14.355	-14.196	-14.108	-14.097
	Reference	Imatinib	Dasatinib	Nilotinib	Ponatinib				
	GScore	-13.156	-10.397	-13.511	-13.187				
E355G	Molecule	**781**	**559**	**558**	**700**	**680**	**646**	**681**	**773**
	GScore	-16.127	-14.737	-14.469	-14.13	-14.059	-13.993	-13.991	-13.956
	Reference	Imatinib	Dasatinib	Nilotinib	Ponatinib				
	GScore	-10.223	-11.005	-13.582	-12.982				
H396A	Molecule	**781**	**751**	**681**	**558**	**559**	**702**	**734**	**766**
	GScore	-15.823	-14.924	-14.874	-14.433	-14.398	-14.225	-14.013	-13.982
	Reference	Imatinib	Dasatinib	Nilotinib	Ponatinib				
	GScore	-13.016	-9.689	-14.12	-13.681				

* In kcal/mol

Results and Discussion

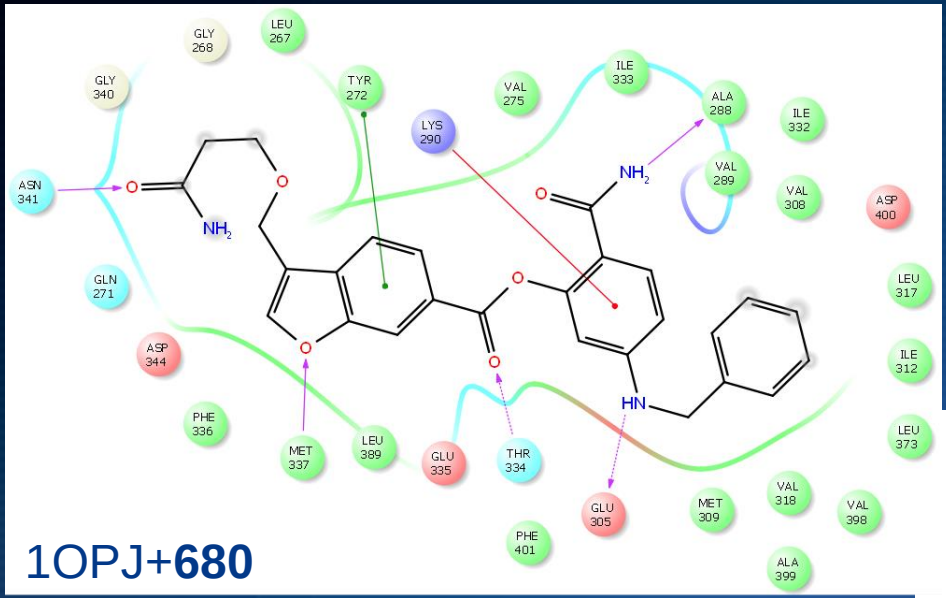
Docking results: interaction energies

Docking results: interaction energies										
Complex	HBondE[a]	LipoE[a]	ElectE[a]	HBond[b]	Good[b]	Bad[b]	Ugly[b]	π-π[b]	π-cation	HBondD[c]
1OPJ+**680**	−3.226	−7.705	−1.061	6	486	9	0	1	1	1.796, 1.890, 1.975, 2.131, 2.167, 2.168
1OPJ+Imatinib	−2.499	−7.270	−1.550	4	516	12	0	1	1	1.711, 1.895, 1.934, 2.005
T315I+**781**	−3.407	−7.540	−0.470	3	482	15	0	1	0	1.900, 2.097, 2.135
T315I+Imatinib	−1.545	−6.835	−1.651	4	563	20	1	1	1	1.548, 1.832, 2.029, 2.099
T315A+**781**	−3.447	−7.759	−0.790	3	447	11	0	1	1	1.754, 2.005, 2.129
T315A+Nilotinib	−1.455	−7.175	−0.829	3	455	7	0	1	0	2.020, 2.031, 2.071
M244V+**723**	−1.988	−7.737	−2.312	4	448	13	0	1	1	1.793, 2.029, 2.096, 2.340
M244V+Nilotinib	−1.610	−7.561	−0.831	3	529	8	0	1	0	1.781, 1.911, 2.225
E355G+**781**	−4.282	−7.545	−1.151	5	462	14	1	1	1	1.662, 1.756, 2.005, 2.058, 2.132
E355G+Nilotinib	−1.653	−7.703	−0.789	3	531	10	0	1	0	1.872, 2.018, 2.108
H396A+**781**	−3.957	−7.593	−1.145	5	457	9	0	1	1	1.675, 1.813, 1.983, 1.986, 2.159
H396A+Nilotinib	−1.795	−7.516	−1.003	3	521	11	0	1	0	1.648, 1.948, 1.970

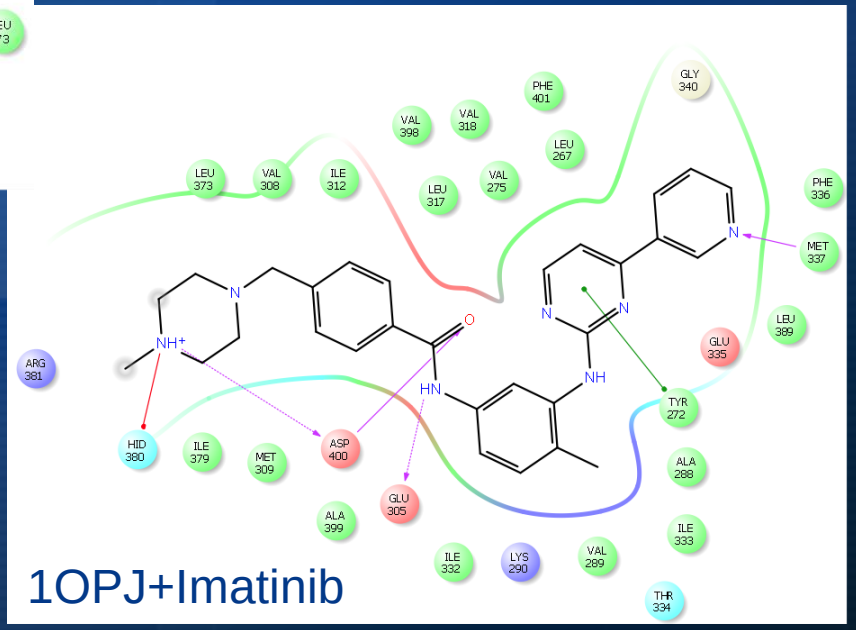
[a] In kcal/mol.
[b] Number of contacts.
[c] H-Bond distances, in Å.

Results and Discussion

Docking: 2D interactions
1OPJ



1OPJ+**680**

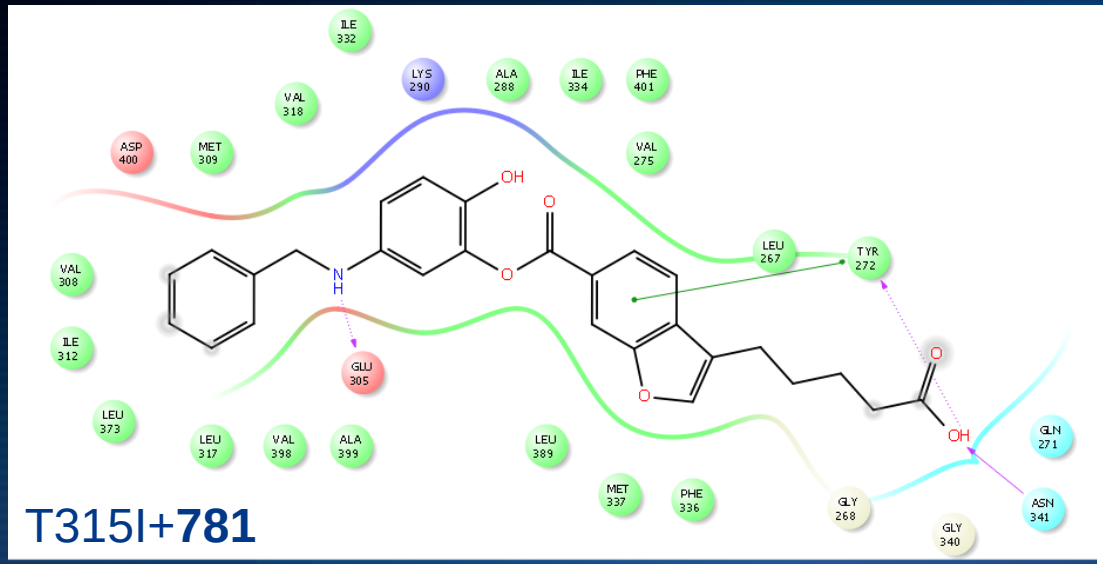


1OPJ+Imatinib

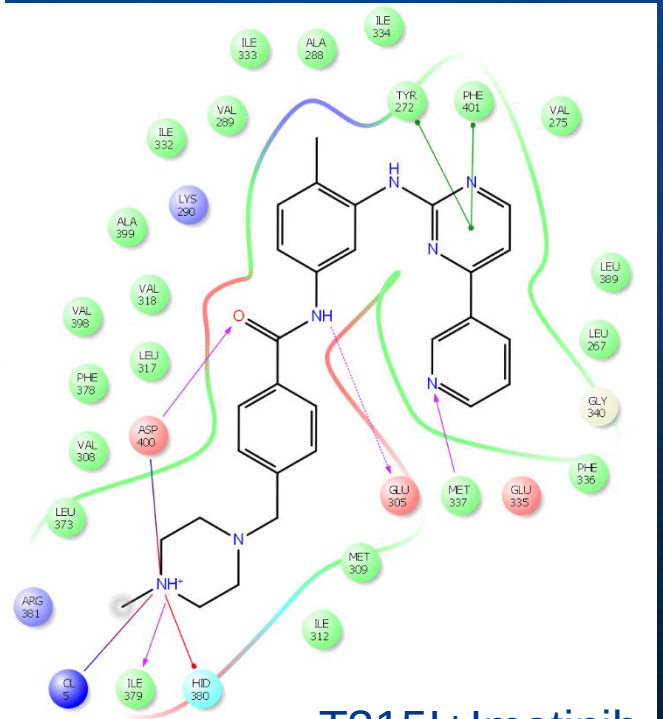
- Charged (negative)
- Charged (positive)
- Polar
- Hydrophobic
- Glycine
- Metal
- Water
- Hydration site
- Displaced hydration site
- π−π stacking
- π−cation
- H-bond (backbone)
- H-bond (side chain)
- Metal coordination
- Salt Bridge
- Solvent exposure

Results and Discussion

Docking: 2D interactions
T315I



T315I+**781**

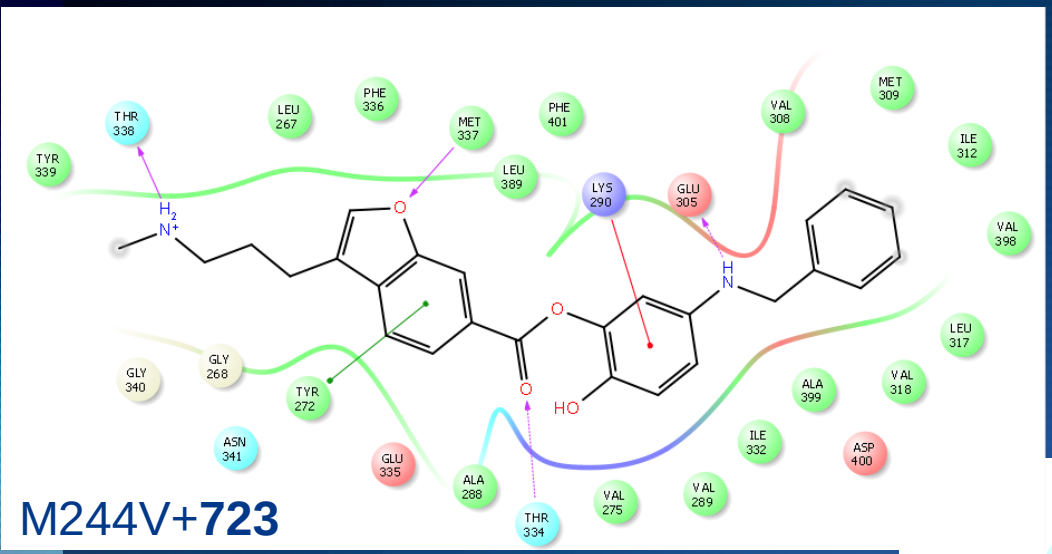


T315I+Imatinib

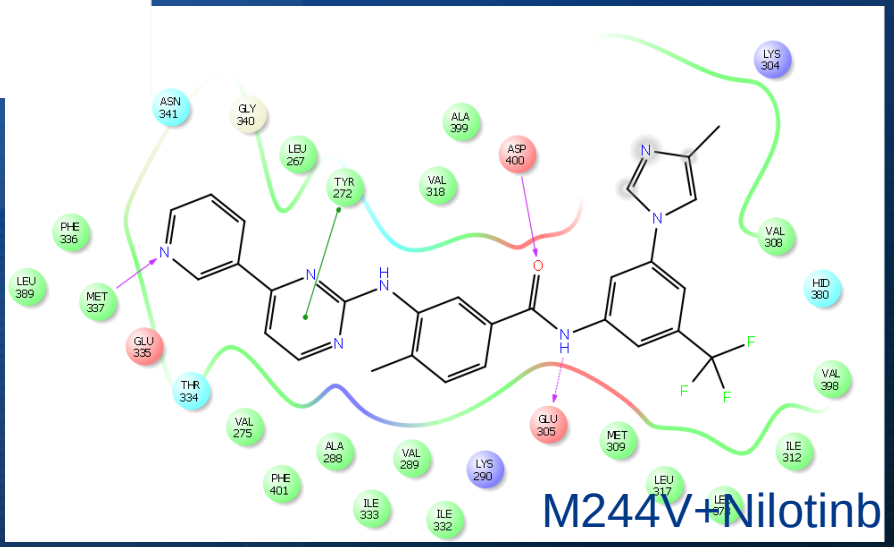
- Charged (negative)
- Charged (positive)
- Polar
- Hydrophobic
- Glycine
- Metal
- Water
- Hydration site
- Displaced hydration site
- π–π stacking
- π–cation
- H-bond (backbone)
- H-bond (side chain)
- Metal coordination
- Salt Bridge
- Solvent exposure

Results and Discussion

Docking: 2D interactions
M244V



M244V+**723**

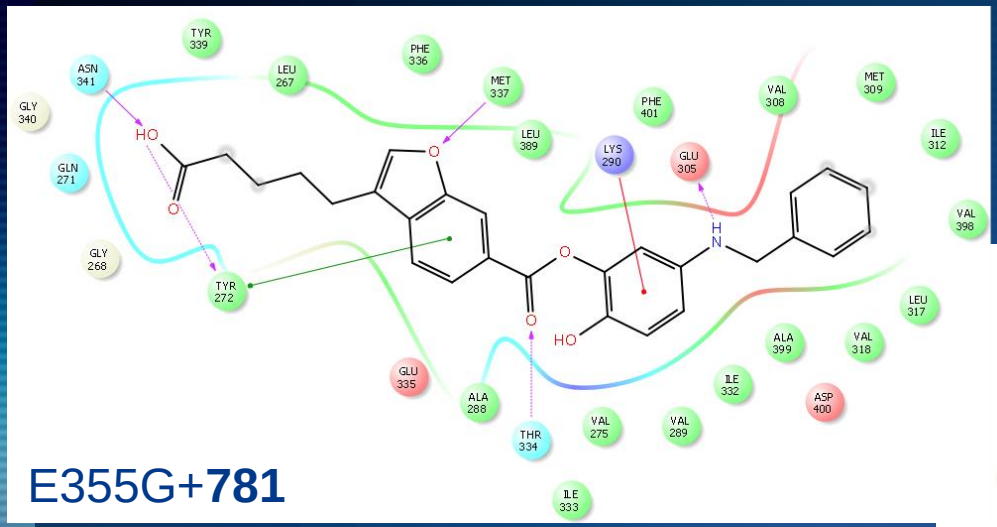


M244V+Nilotinb

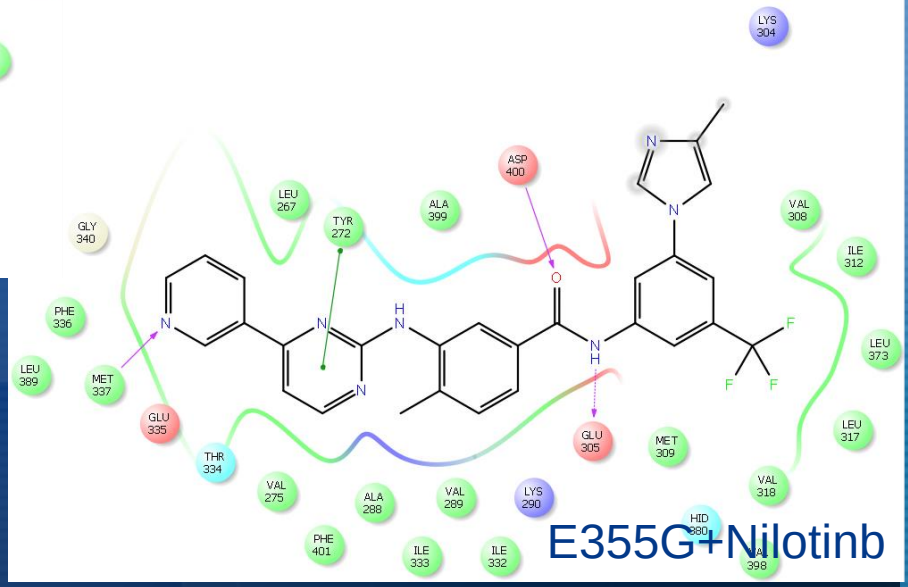
- Charged (negative)
- Charged (positive)
- Polar
- Hydrophobic
- Glycine
- Metal
- Water
- Hydration site
- Displaced hydration site
- π−π stacking
- π−cation
- H-bond (backbone)
- H-bond (side chain)
- Metal coordination
- Salt Bridge
- Solvent exposure

Results and Discussion

Docking: 2D interactions E355G



E355G+**781**

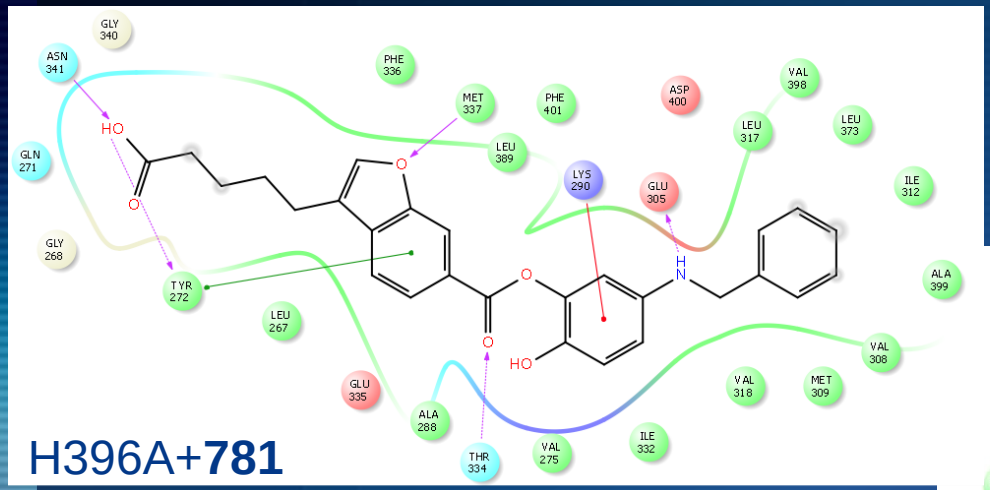


E355G+Nilotinb

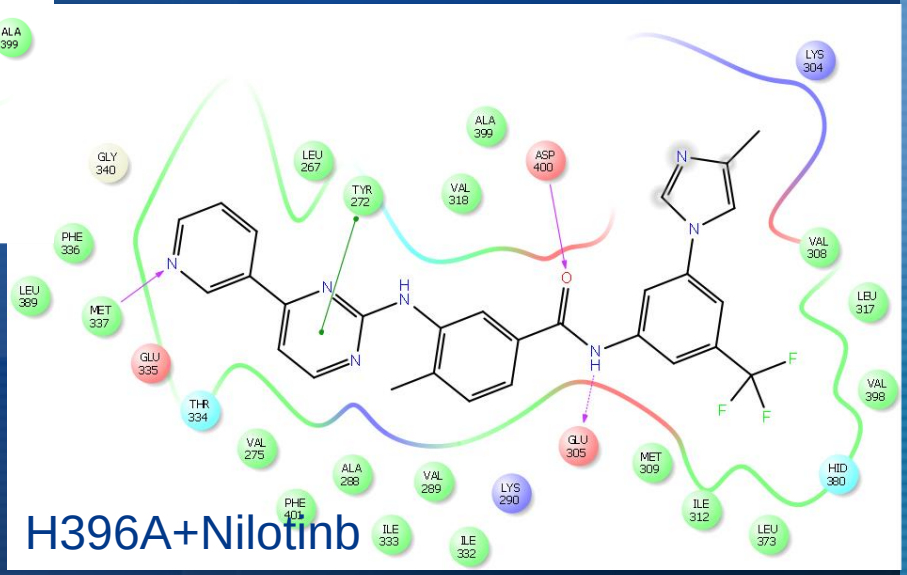
- Charged (negative)
- Charged (positive)
- Polar
- Hydrophobic
- Glycine
- Metal
- Water
- Hydration site
- Displaced hydration site
- π-π stacking
- π-cation
- H-bond (backbone)
- H-bond (side chain)
- Metal coordination
- Salt Bridge
- Solvent exposure

Results and Discussion

Docking: 2D interactions H396A



H396A+**781**



H396A+Nilotinb

- 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

Conclussion

- 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

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