olecular dynamics refinement and scoring in WISDOM virtual screenin

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tein Flexibility and Mobility
Structure-Based Drug Design

ally Structure-Based Drug Design was based on the “lock and key” m

ny targets show significant flexibility upon ligand binding (e.g. local
rrangement of side-chains or small motions of loops)

ctive methods are available for docking a flexible ligand into a rigid ta

vadays there are efforts to consider protein flexibility and mobility in d
gn approaches

approach is based on molecular dynamics

y Molecular Dynamics?

provide the “gold standard” when used to describe flexible biomolecu
ems

permit the simultaneus simulation of either target and/or ligands flexib

simulations can take in account solvent contribution to the system en

can be chosen to validate and refine the orientations of docked
npounds and rescore them using a reliable scoring function

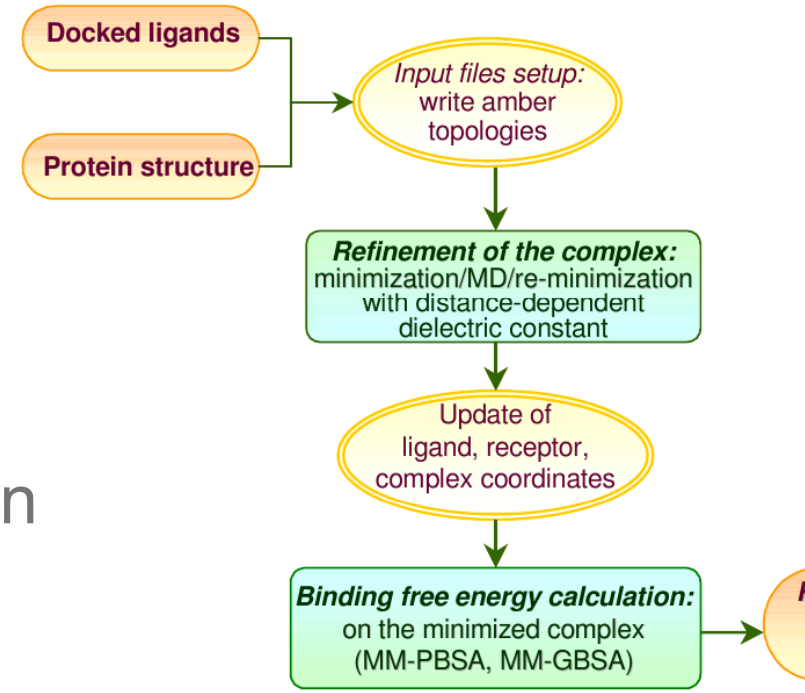
these reasons MD can be chosen to validate and refine the orientatio
ked compounds and rescore them using a reliable scoring function

w to refine and rescore docking complexes using M

Refinement and Rescoring procedure based on MM/MD and MM-PBS
s been designed and then validated

ltistep protocol:

- Minimization of ligand-target complexes
- MD simulation of minimized complexes
- Minimization of complexes after MD
- Free energy of binding (ΔGbind) estimation with MM-PBSA and/or MM-GBSA

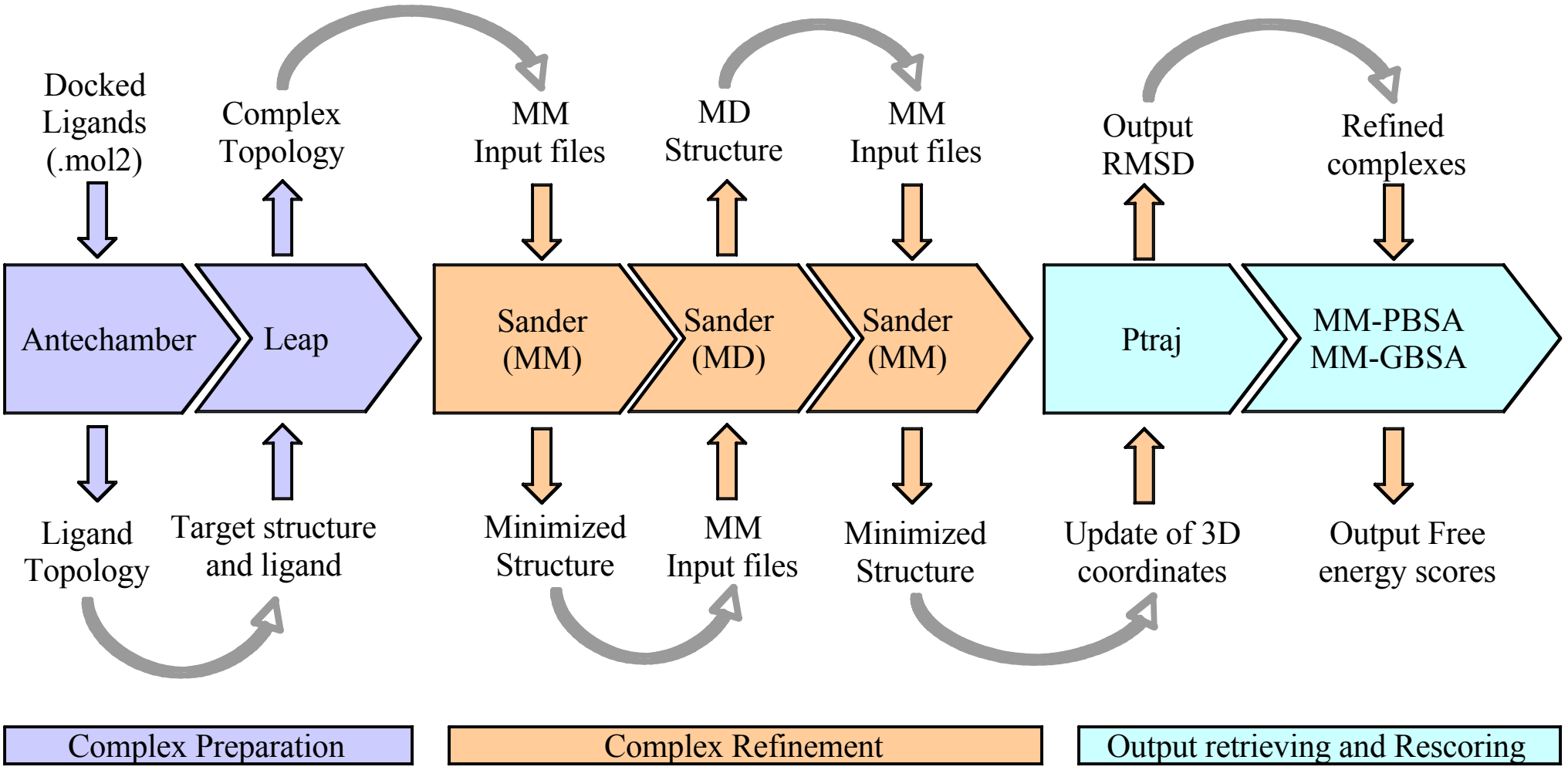


Ligand + Target ⟷ Co

$$\Delta G_{binding} = \Delta E_{MM} + \Delta G_{solv}$$

ΔE_{MM} = interaction energy in vacu

cedure in a virtual screening?



-Refinement/Rescore Procedure Validation

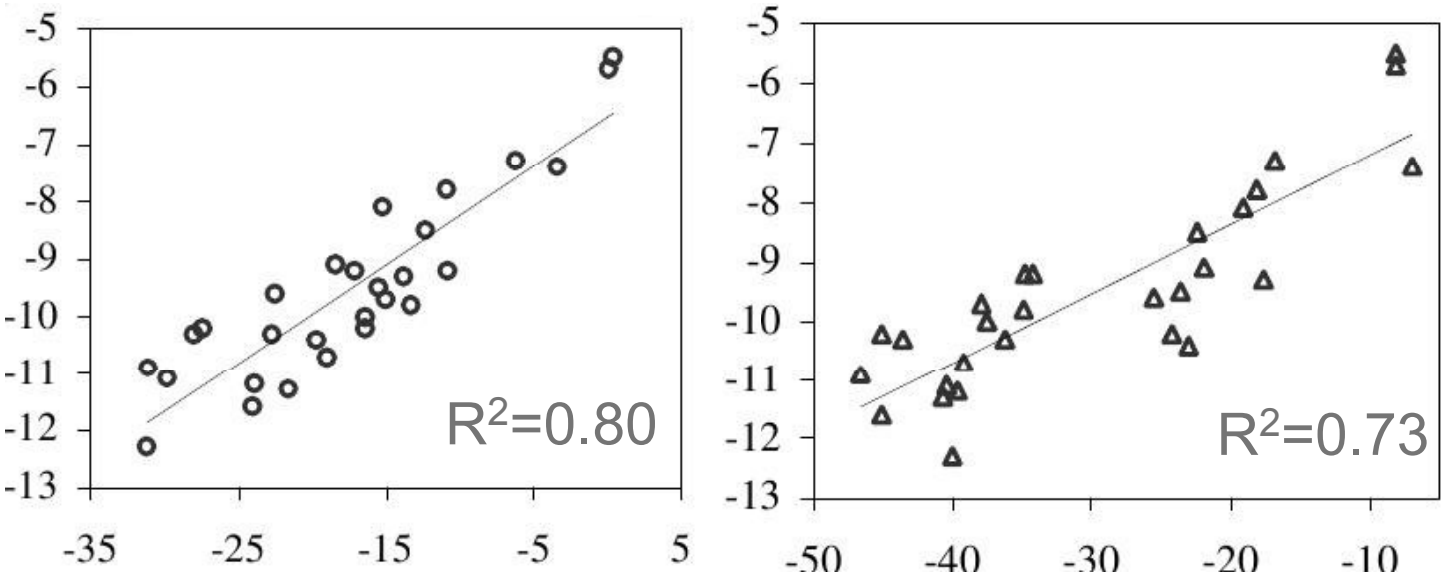
elli et al. *Bioorganic & Medicinal Chemistry* - 15, 2007 (7865-7877)

get: Aldose reductase

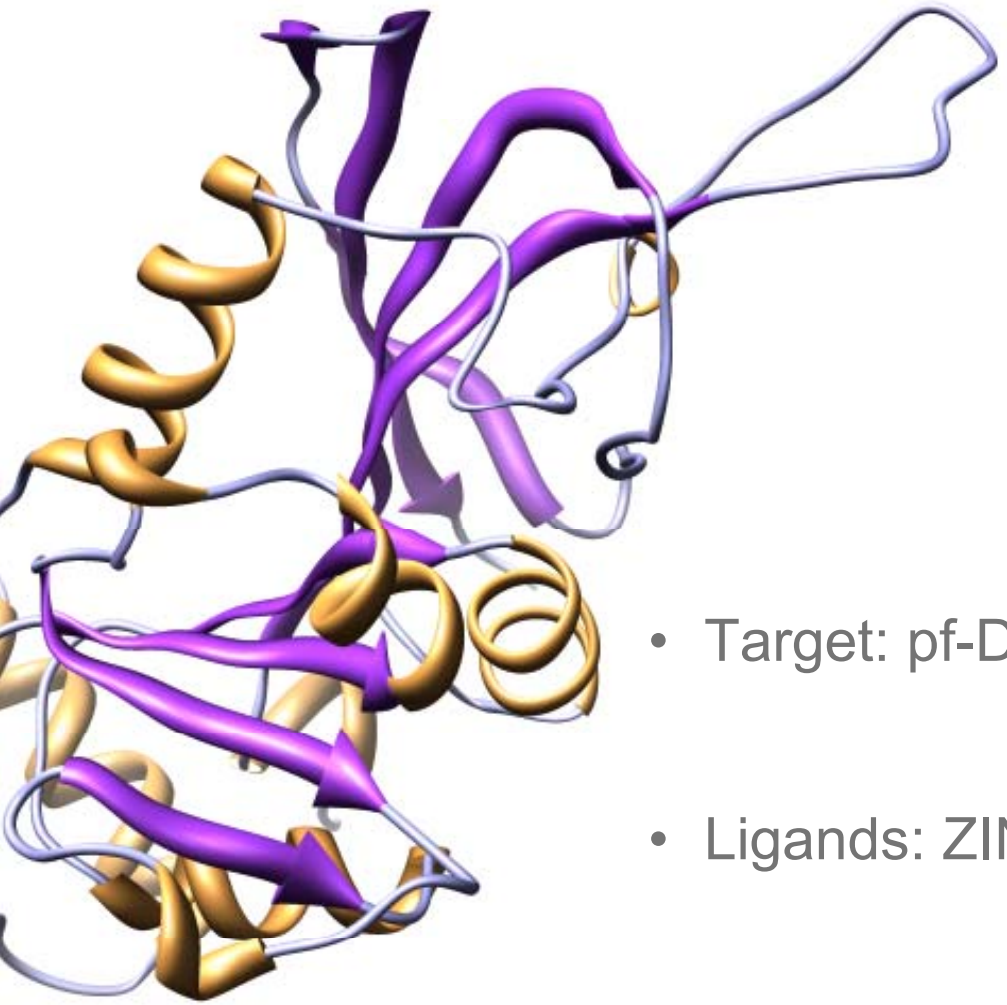
nds: 28 known inhibitors with measured activities and known binding
des

dicted free energy of binding show good correlation with experimental

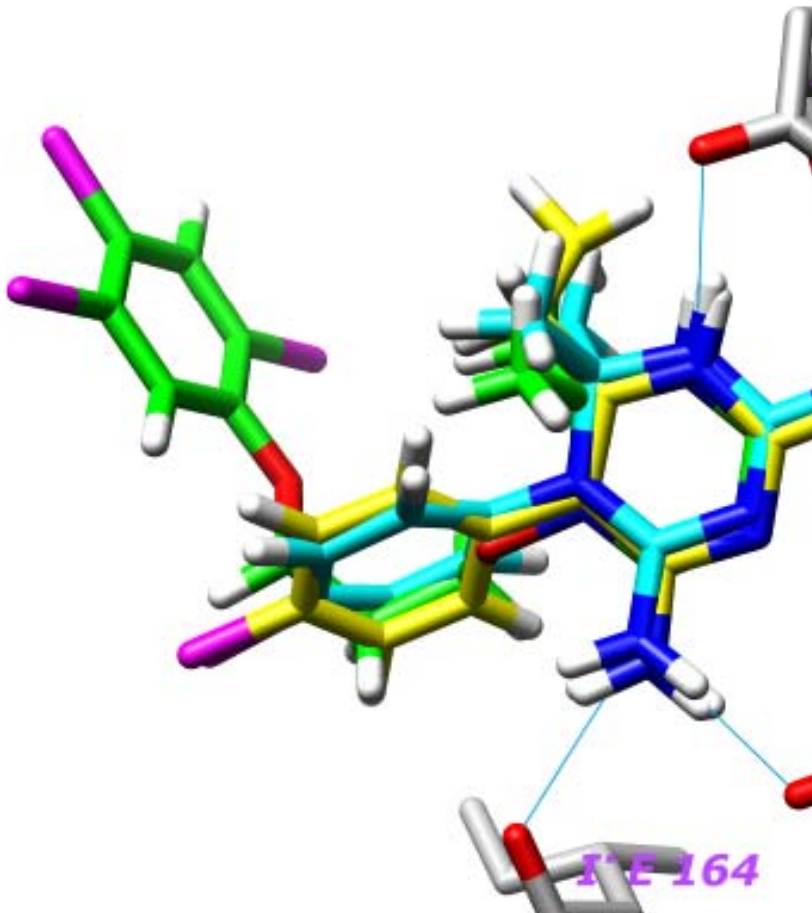
-PBSA estimated free energies of binding are the best correlating



ractical example



- Target: pf-DHFR
- Ligands: ZINC-DB
- Docking: FlexX
- MD-Refinement

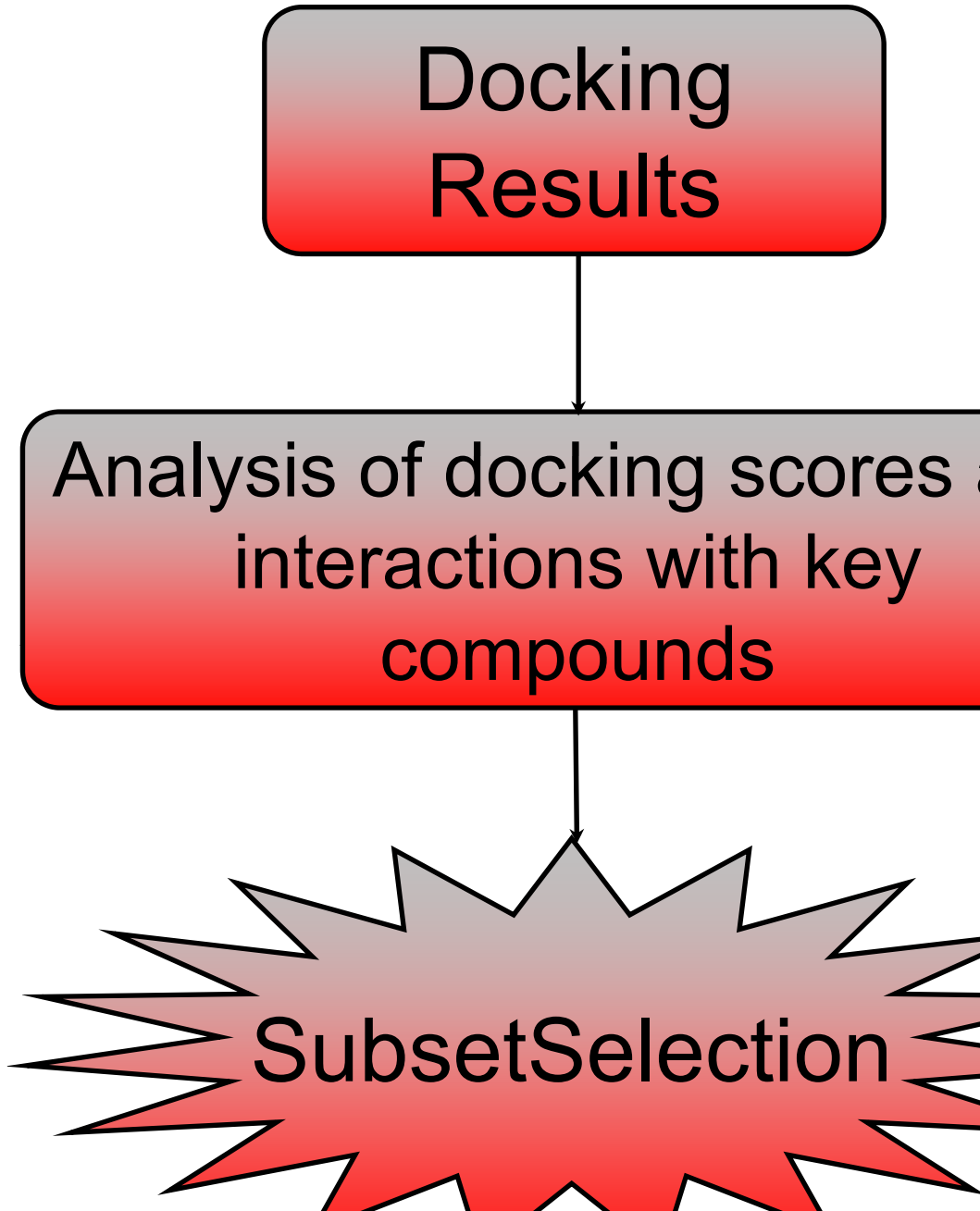


cking Results Analysis

npounds ranking based
docking energy score

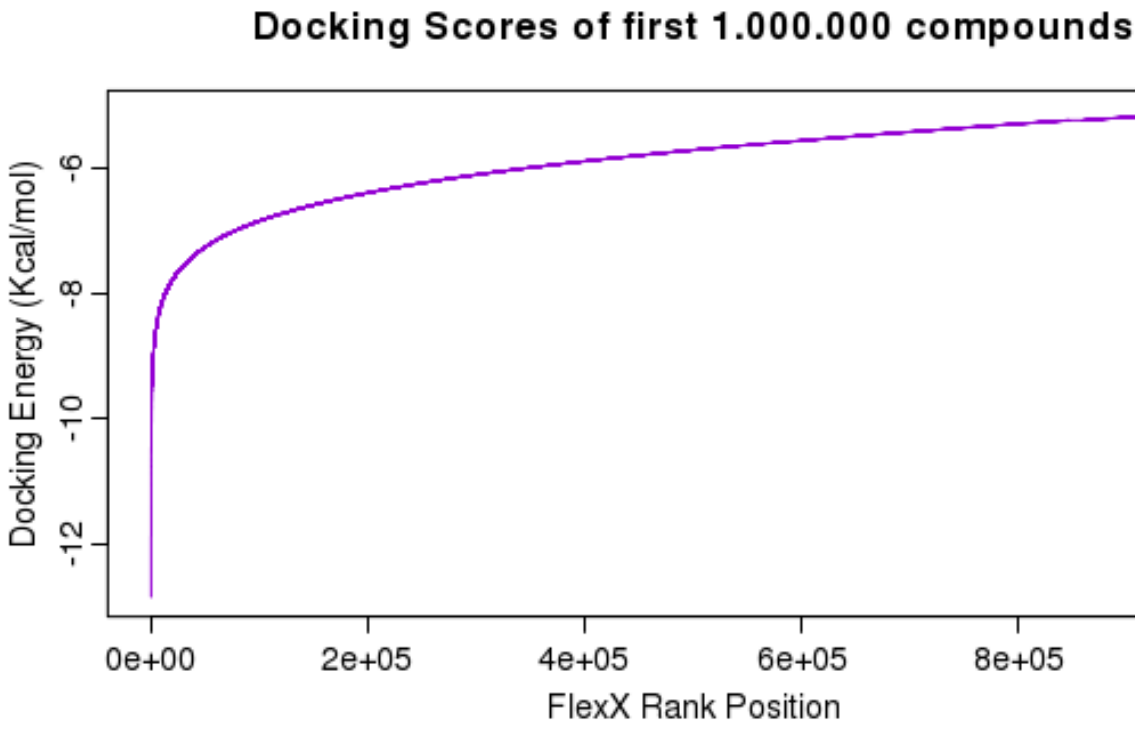
lysis of interactions
ablished by each ligand
aminoacids of pf-DHFR
ling site

ection of a subset of
npounds to be refined
g the MD-refinement
cedure

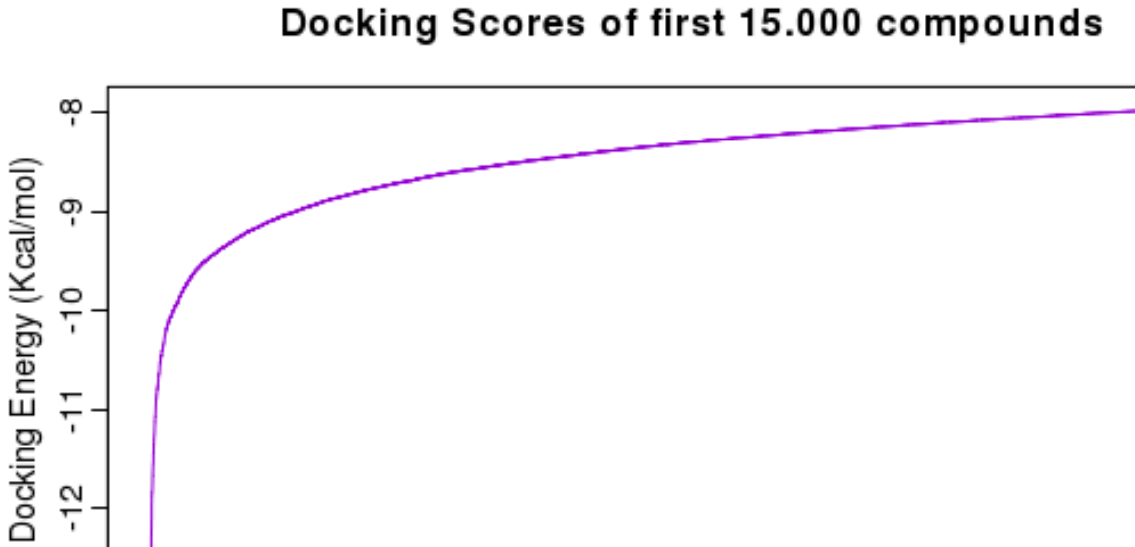


cking energy evaluation

lysis of Docking energy
d of first million ranked
npounds



lysis of Docking energy
d with a cutoff of ~-8 Kcal
-1



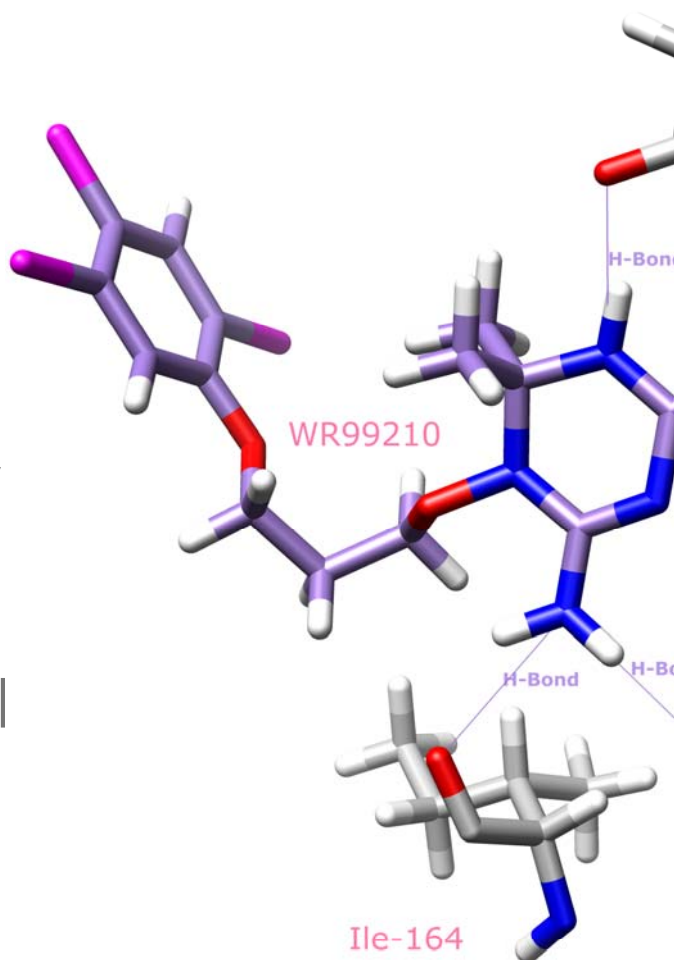
alysis of docked compound interactions

alysis of hydrogen bond among known inhibitors
target

99210 establishes hydrogen bonds with Asp54
4 and Ile164

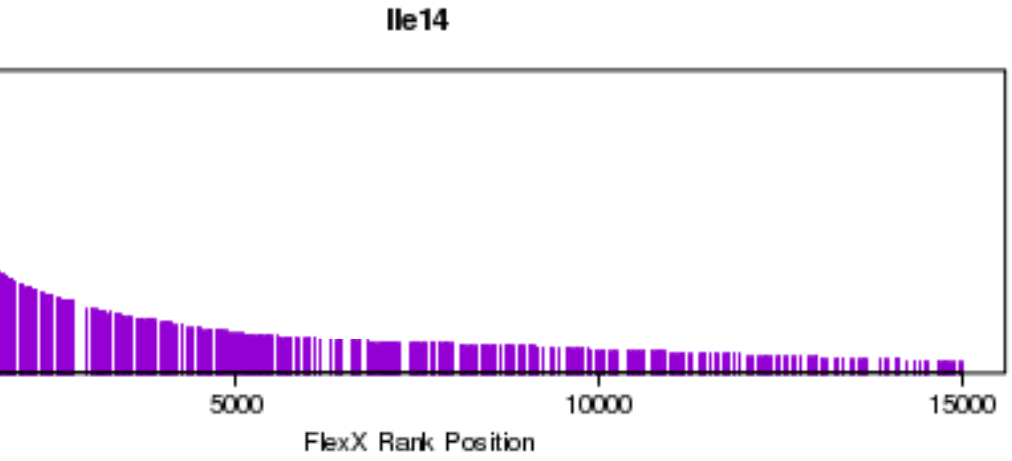
ection of I14, D54, I164 as binding site key
dues and calculation of their relative frequency
ond with ligands

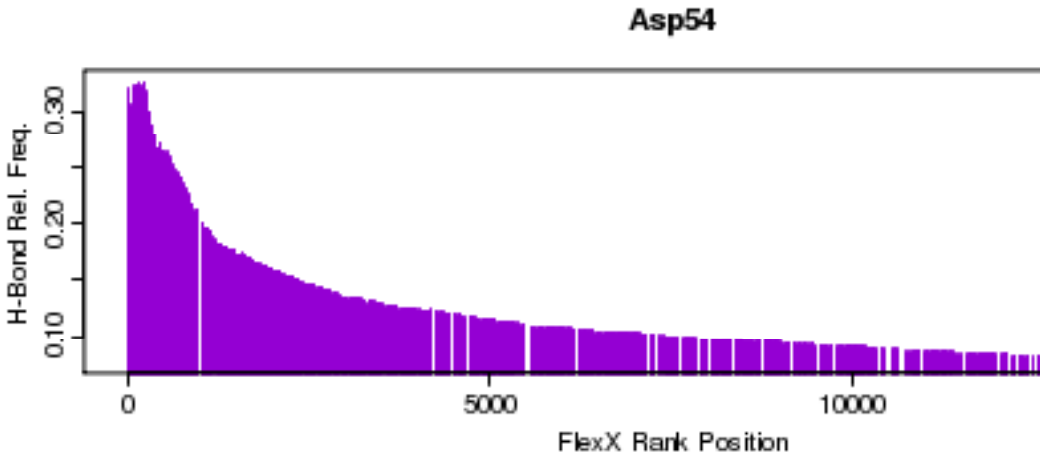
ond frequency were calculated using the follow
nula, where:
compound rank position
1 or 0 whether compound i interact or not with I
dues

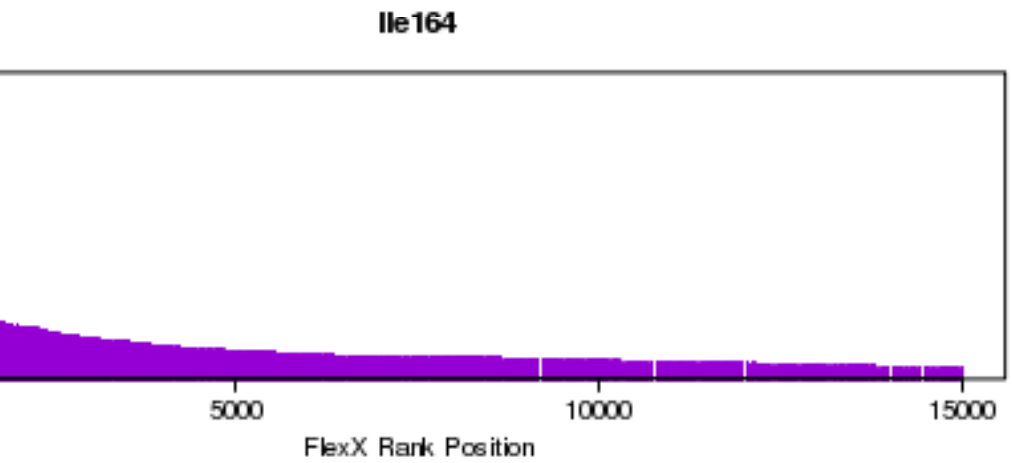


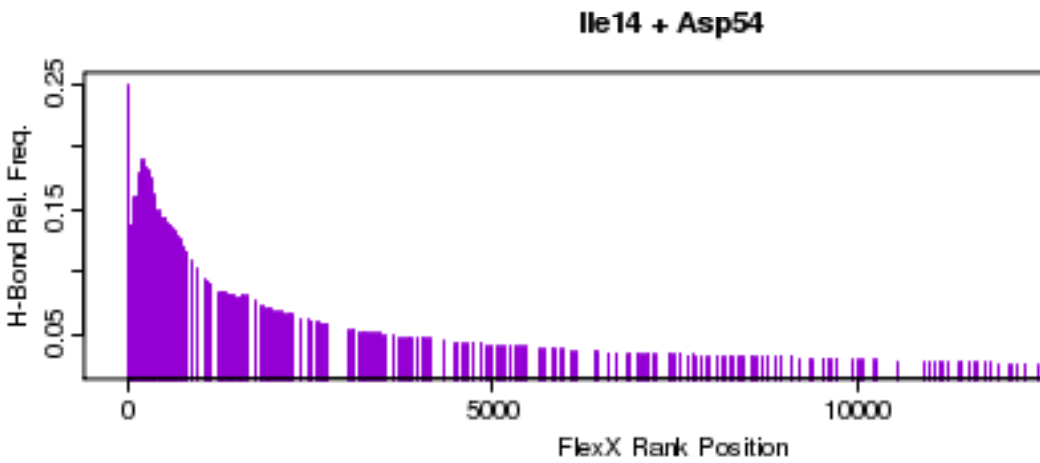
$$\sum^{n} \frac{a_i}{}$$

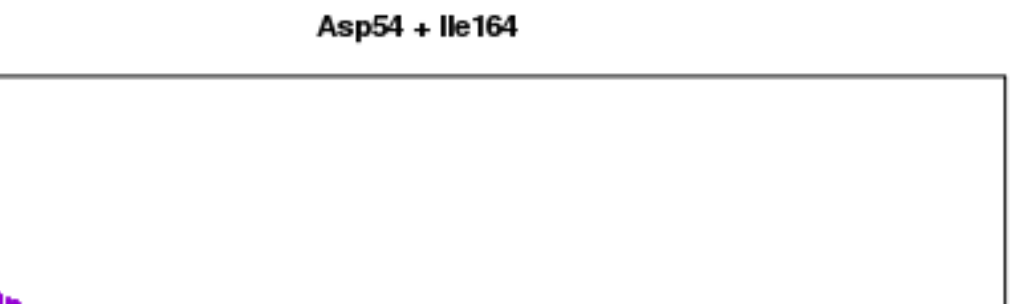
drogen bond frequency analysis

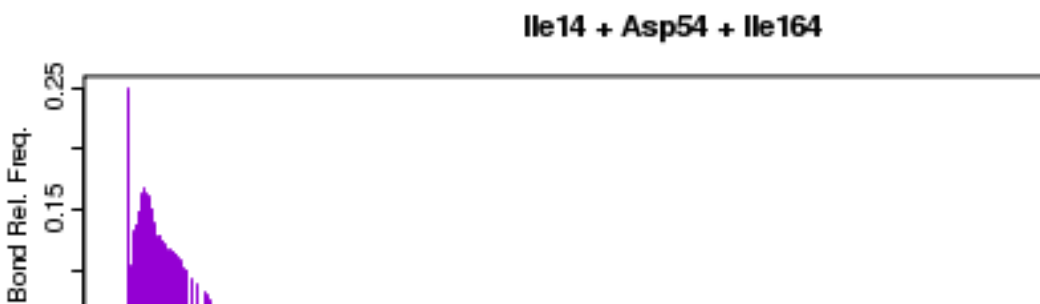












Refinement preparation

ection of first 15.000 compounds from the docking scores ranked list

npounds partial charges calculation

npounds separated by total charge (Insight)

tial atomic charges calculated with AM1-BCC (Antechamber)

ation of 300 packages containing 50 compounds

rage of created packages on SE

ing of input files

alysis of MD Refinement Results

ranking of compounds according to MM-PBSA and evaluation
ee energy of binding

lysis of interaction focusing on H-Bond among ligands and
54, Ile14 and Ile164

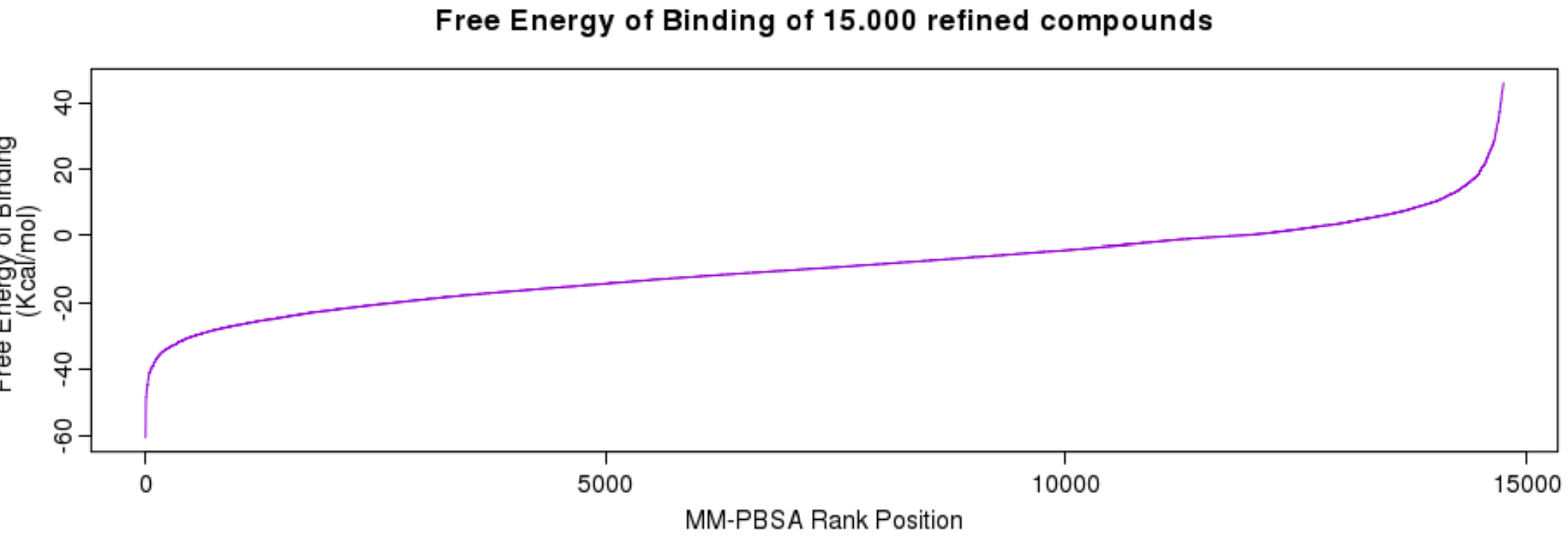
ualisation of best scoring compounds

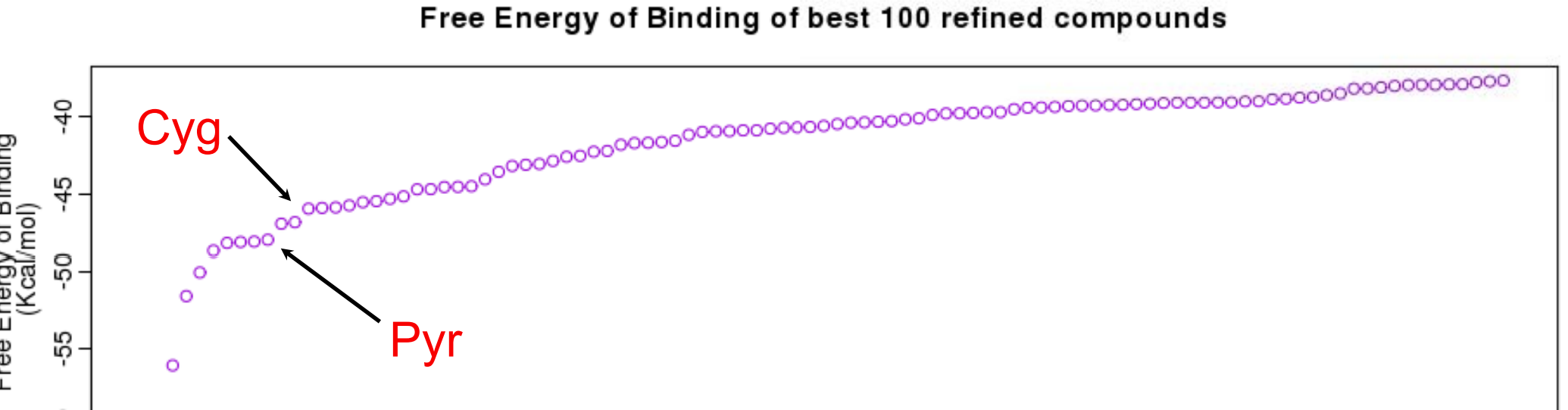
Evaluation of mobility after MD

Evaluation of binding orientation, comparison with WR99210

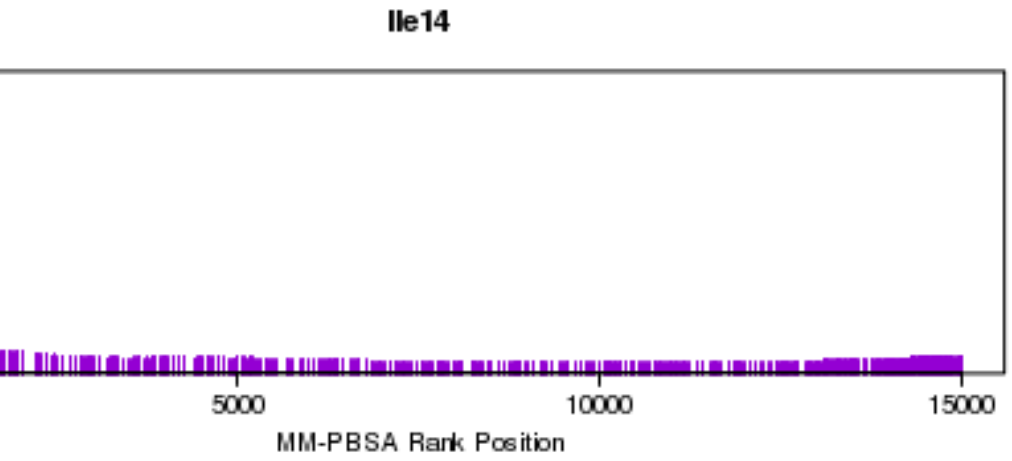
luation of rank position difference between docking score and

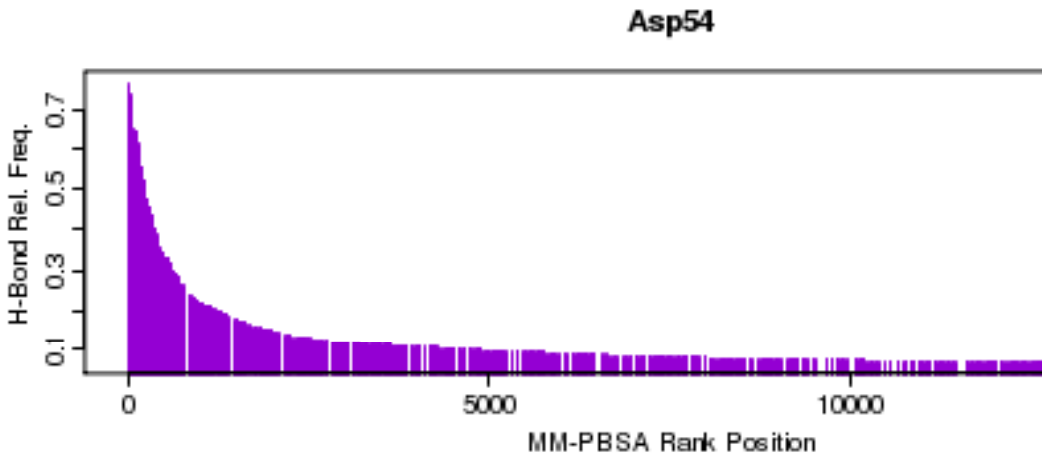
-PBSA Rescore Results

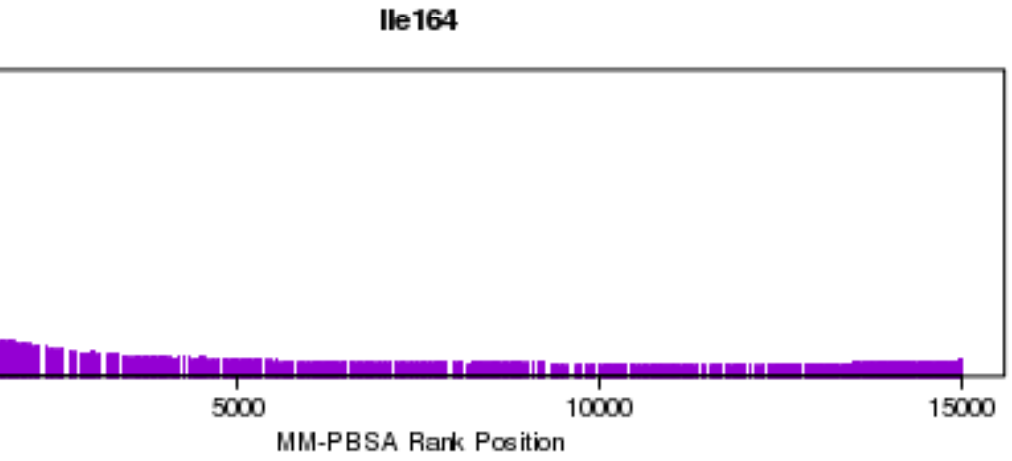


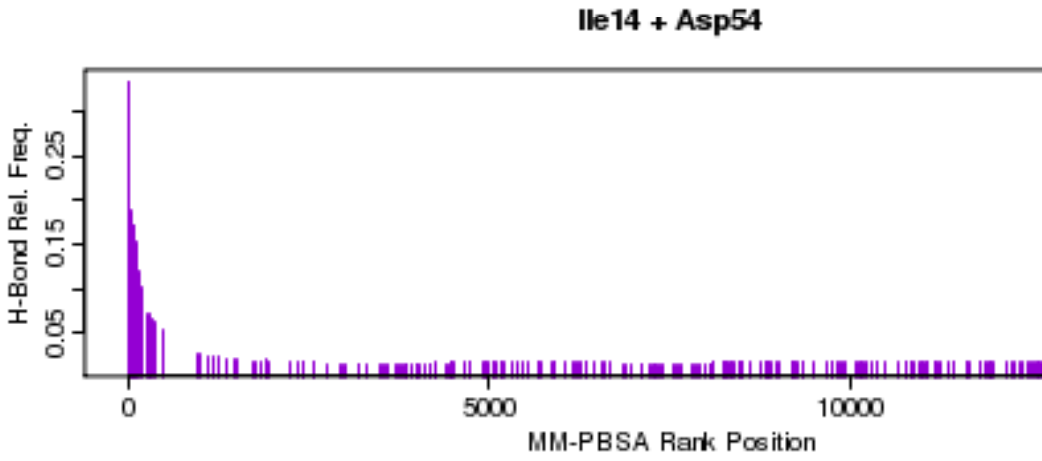


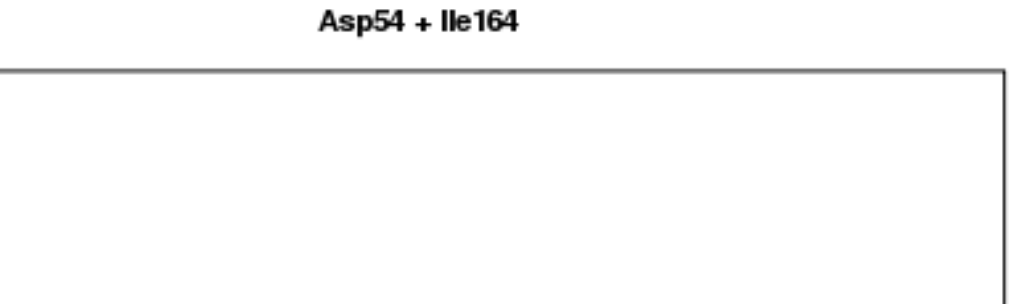
eraction frequencies after MD-Refinement

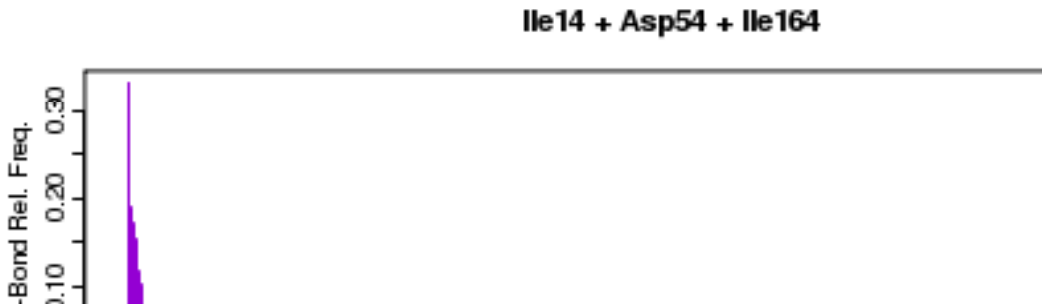












ucture visualization analysis

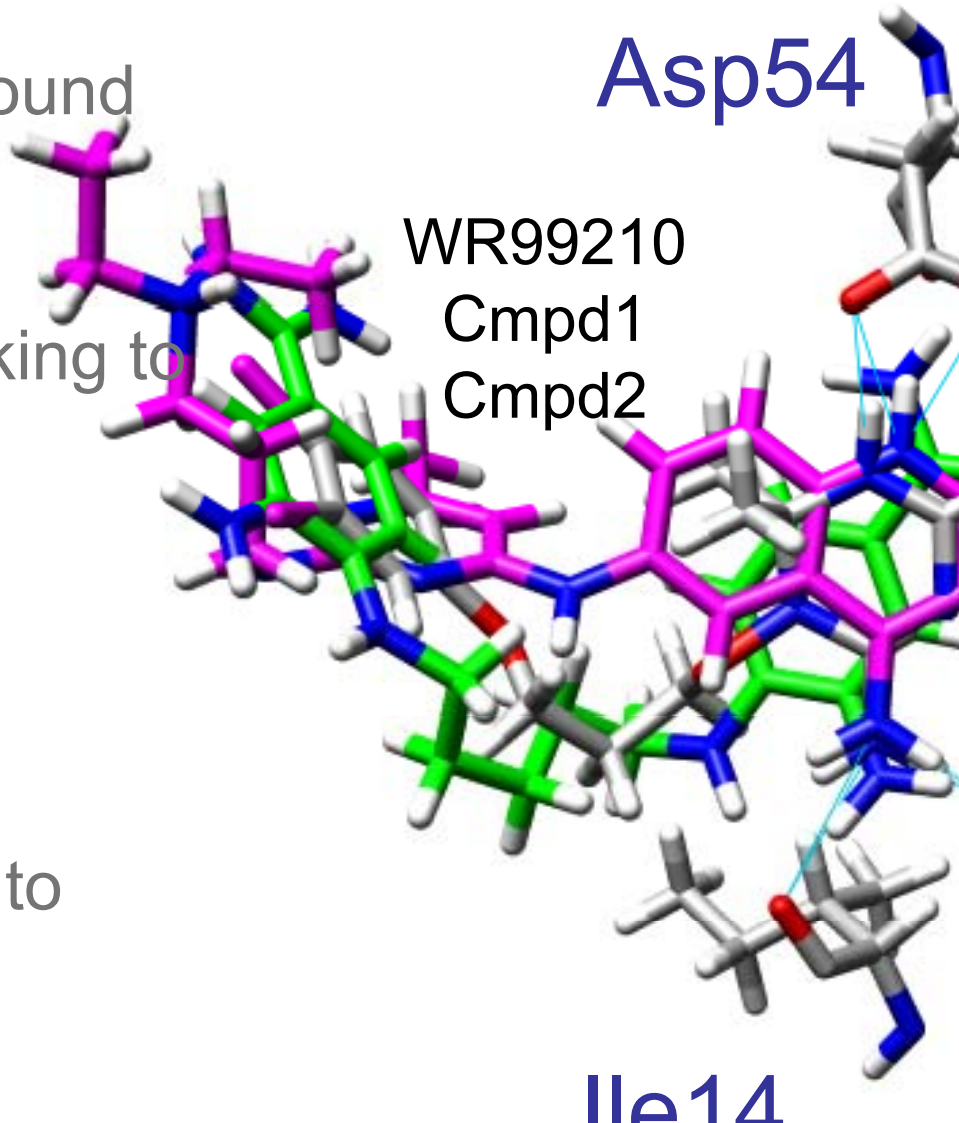
nplexes of first 100 compounds were
alized

nparison among WR99210 and compound
ntations

lysis of compounds mobility from docking to
t refinement complexes

lysis of interactions with binding site
dues

n part of compounds interact similarly to
99210



alysis of rank position variations

rix of compound rank position
ations from docking to MM-
SA

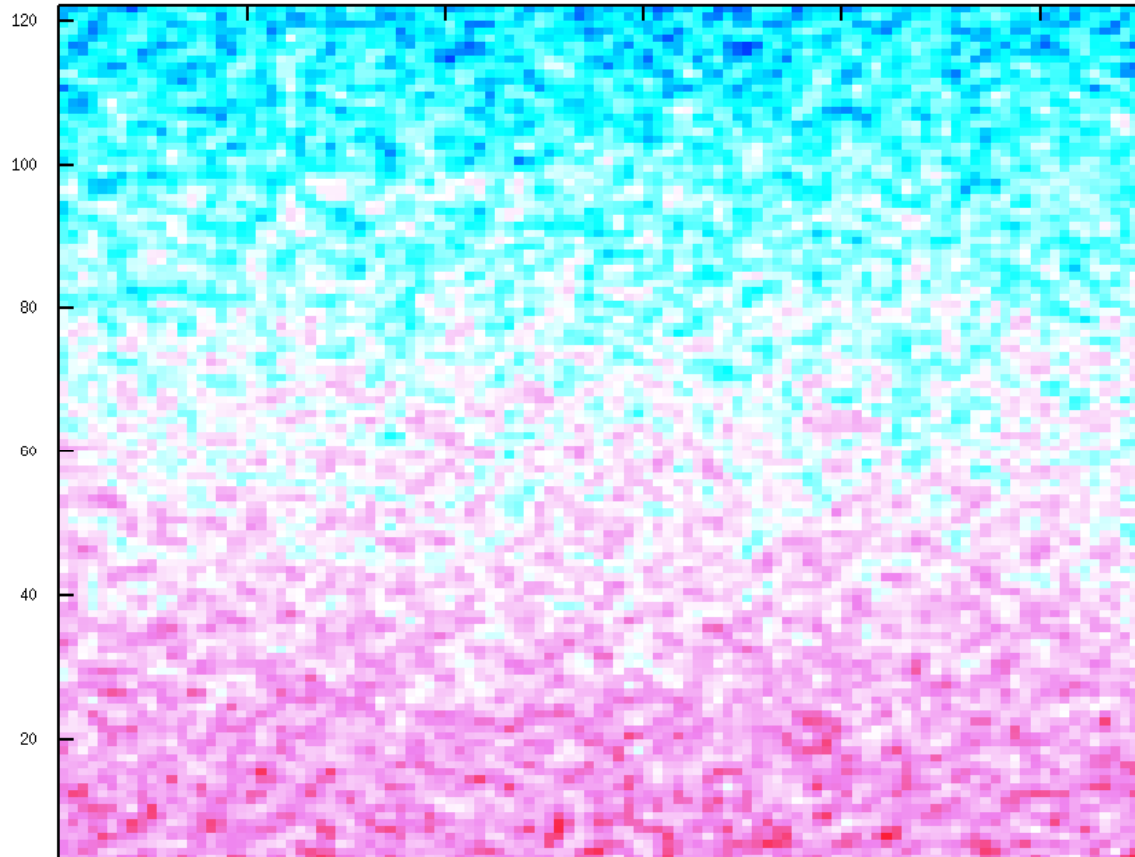
sition = #MM-PBSA - #Dock

ults have been plotted
wing the order of MM-PBSA
ked list

rix was filled by column from
to right starting at the bottom

values mean compounds on
top of the MM-PBSA list but
he bottom of the FlexX list

Last co
inMM-PB
l



nclusions

ecular dynamics efficiently refined the orientation of docked compoun

-PBSA rescoring permitted to estimate the free energy of binding of th
ked compounds

lying the MD-refinement/rescoring procedure, some compounds were
overed from the tail of docking ranked list, while others moved from th
d to the tail of MM-PBSA ranked list

resting molecules were retrieved among the first 100 best scored
npounds, and several of these will be selected for in vitro activity assa

knowledgement

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t. Anna Maria Ferrari

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