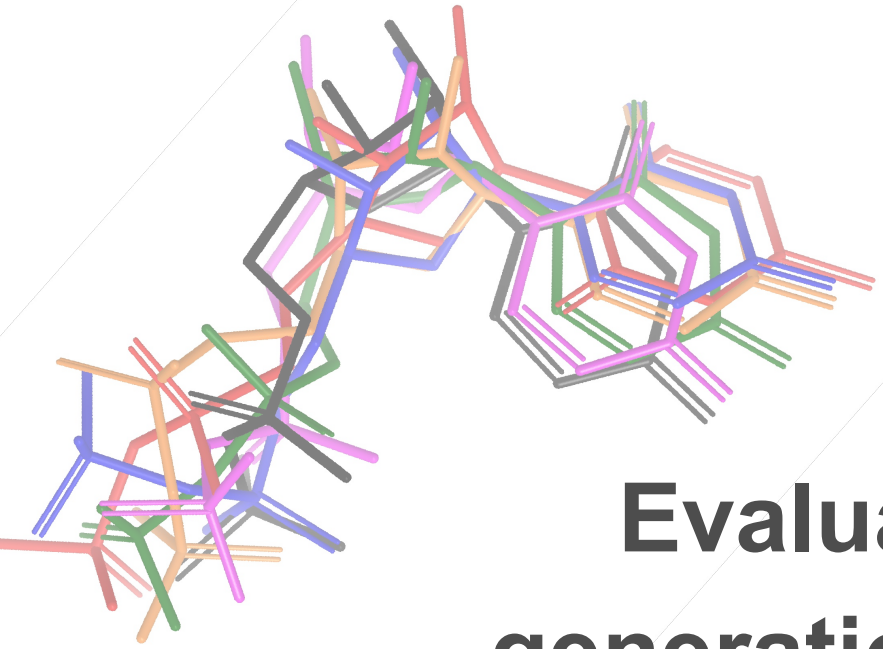

UNIVERSITAT ROVIRA I VIRGILI

Evaluation of conformer generation tools to reproduce bioactive conformations

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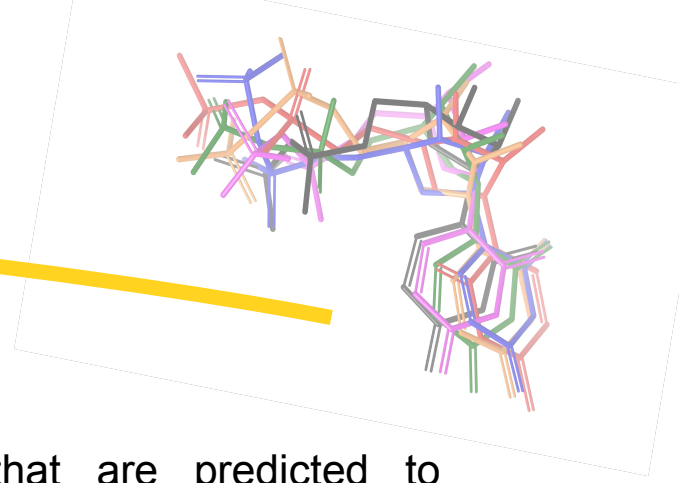
INTRODUCTION

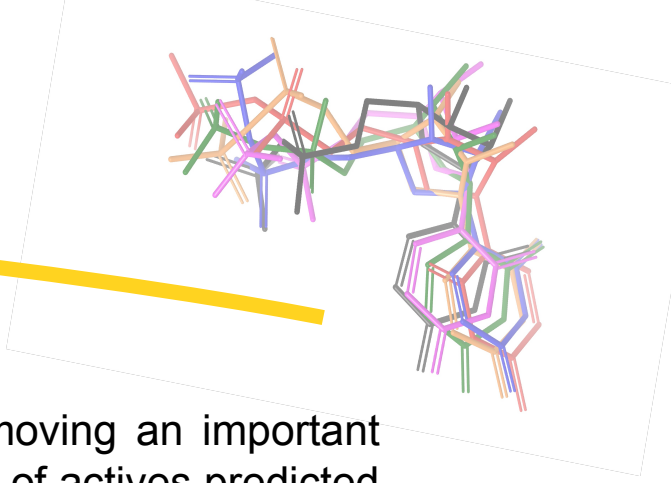


VIRTUAL SCREENING

To find molecules that are predicted to modulate the bioactivity of targets that are relevant for disease prevention and/or treatment

Removing an important part of actives predicted as inactives because of simple criteria

INTRODUCTION



VIRTUAL SCREENING

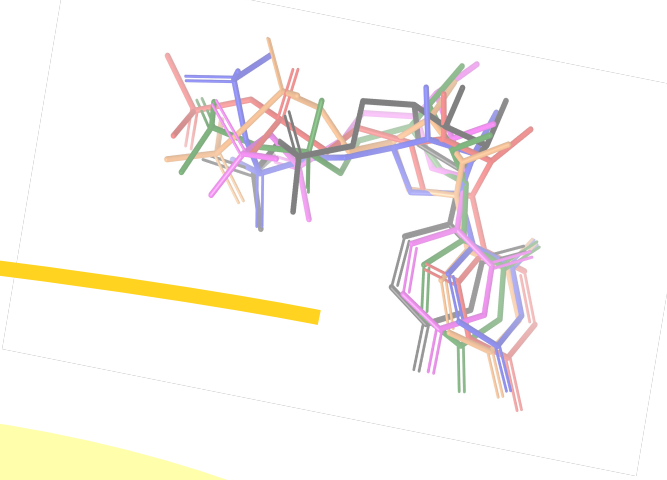
Removing an important part of actives predicted as inactives because of simple criteria

NEED TO IMPROVE

Reduce false negatives

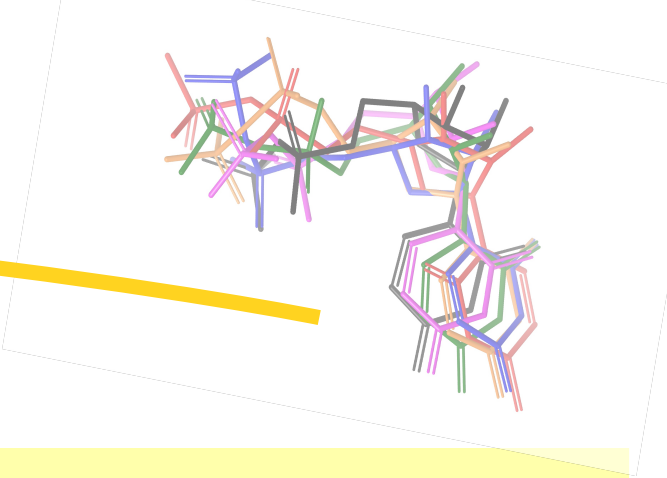
Improve speed of calculations

INTRODUCTION



to explore **the conformational space** available for each *active* candidate without the restrictions imposed by the protein environment

OBJECTIVES



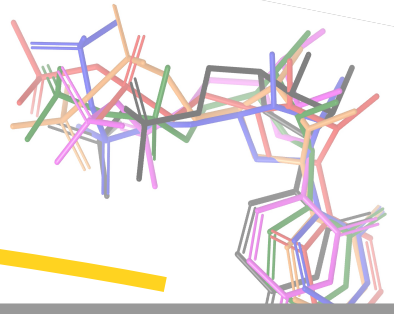
THE MAIN GOALS

(1)To find optimal conditions for conformational sampling with XedeX.

(2)To identify to which extend available tools for conformational sampling are able to reproduce bioactive conformers

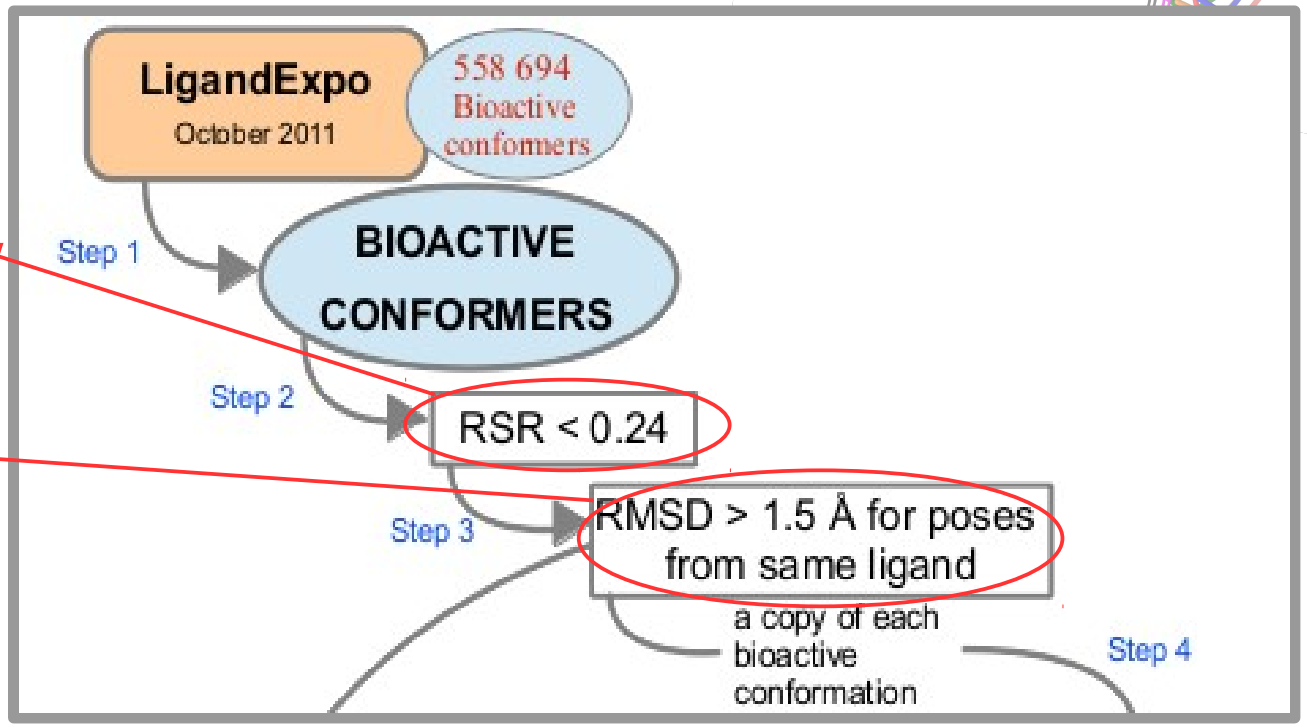
(3)To determine what is the best way of sampling the conformational space and which are the limitations of such approach

METHODOLOGY



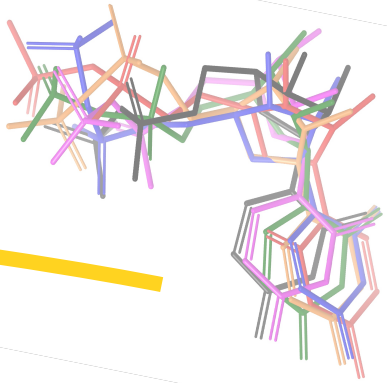
Validated the fitting of the inhibitor to the EDM

Remove redundant conformers



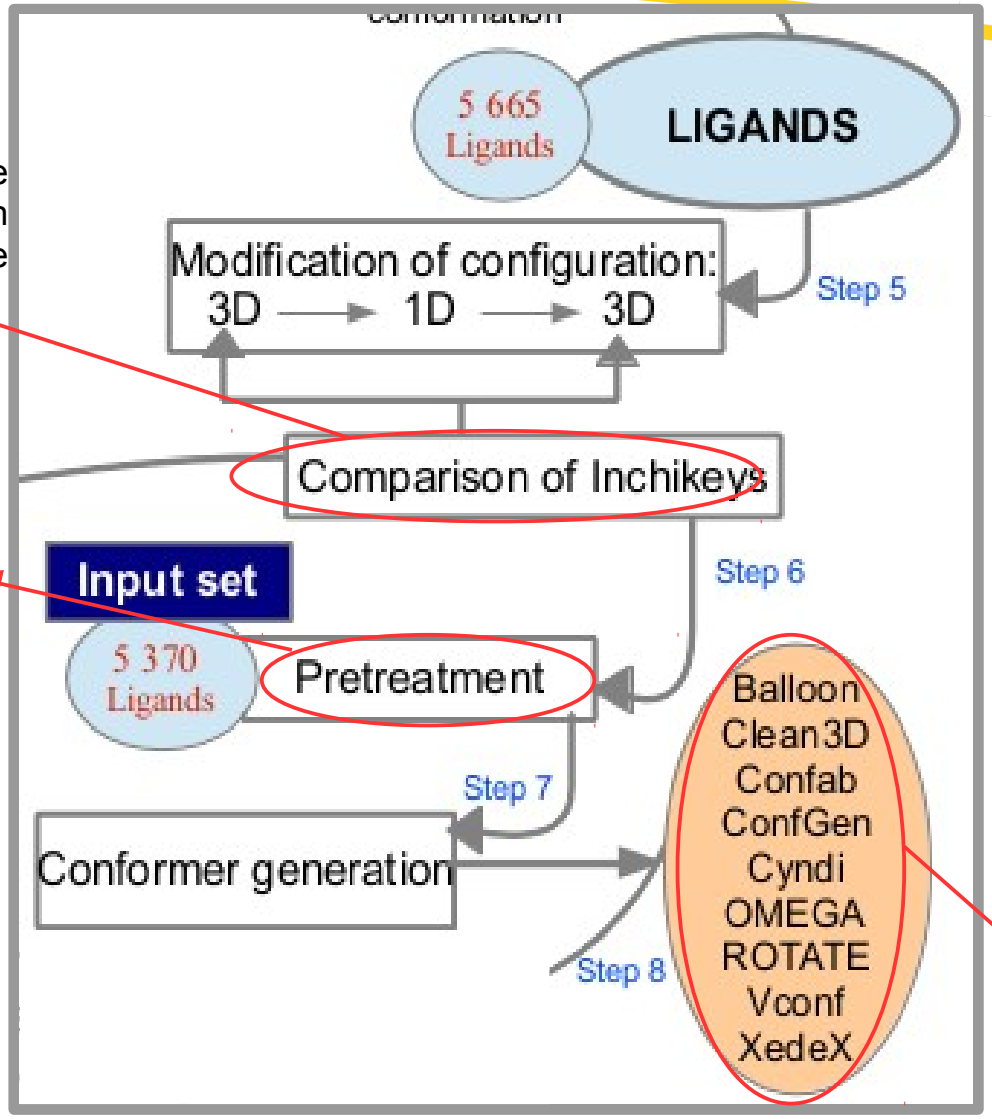
Step 1. Bioactive poses from experimental protein-ligand complexes were download.
Step 2. Poses with Real Space R-value (RSR) equal or higher than 0,24 were removed with the help of VHELIBS.
Step 3. Redundant conformers with RMSD ≤ 1.5 A were removed.
Step 4. The resulting set is formed by 6431 non-duplicated and high-quality conformers that belongs to 5665 different ligands.

METHODOLOGY



To not biasing the conformer generation and to not lose stereochemical information

To ensure the homogeneity of the results



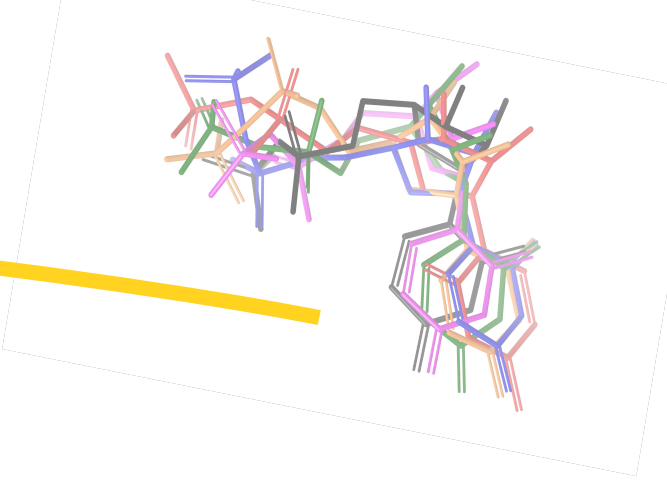
Step 5. With the aim of not biasing the generation of conformers by the input conformation, a modification of coordinates hasdone.

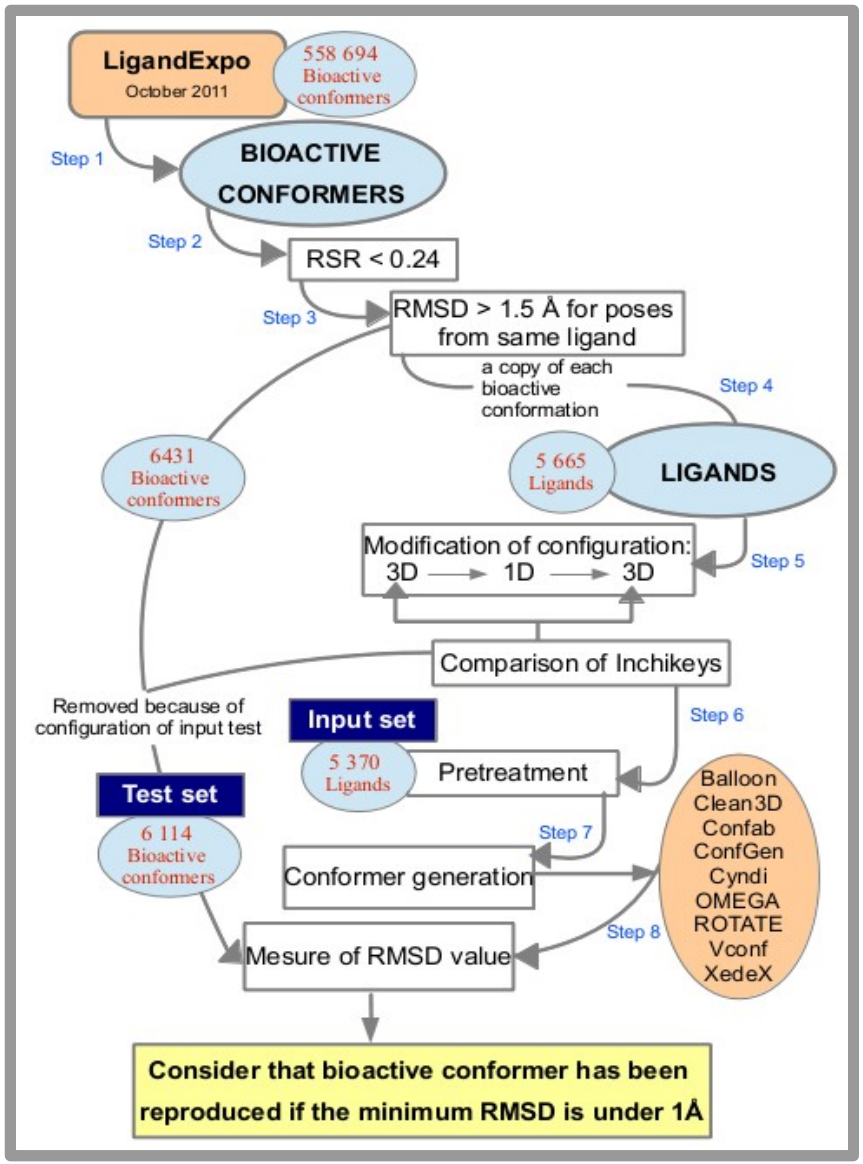
Step 6. To not lost stereochemical information, Inchikeys were compared.

Step 7. Conformer generation by 8 softwares.

Following default parameters or settings recommended

METHODOLOGY





Step 8. Comparison of RMSD value between confomations and Test set

RESULTS

Success to reproduce the bioactive conformation by different XedeX setttings

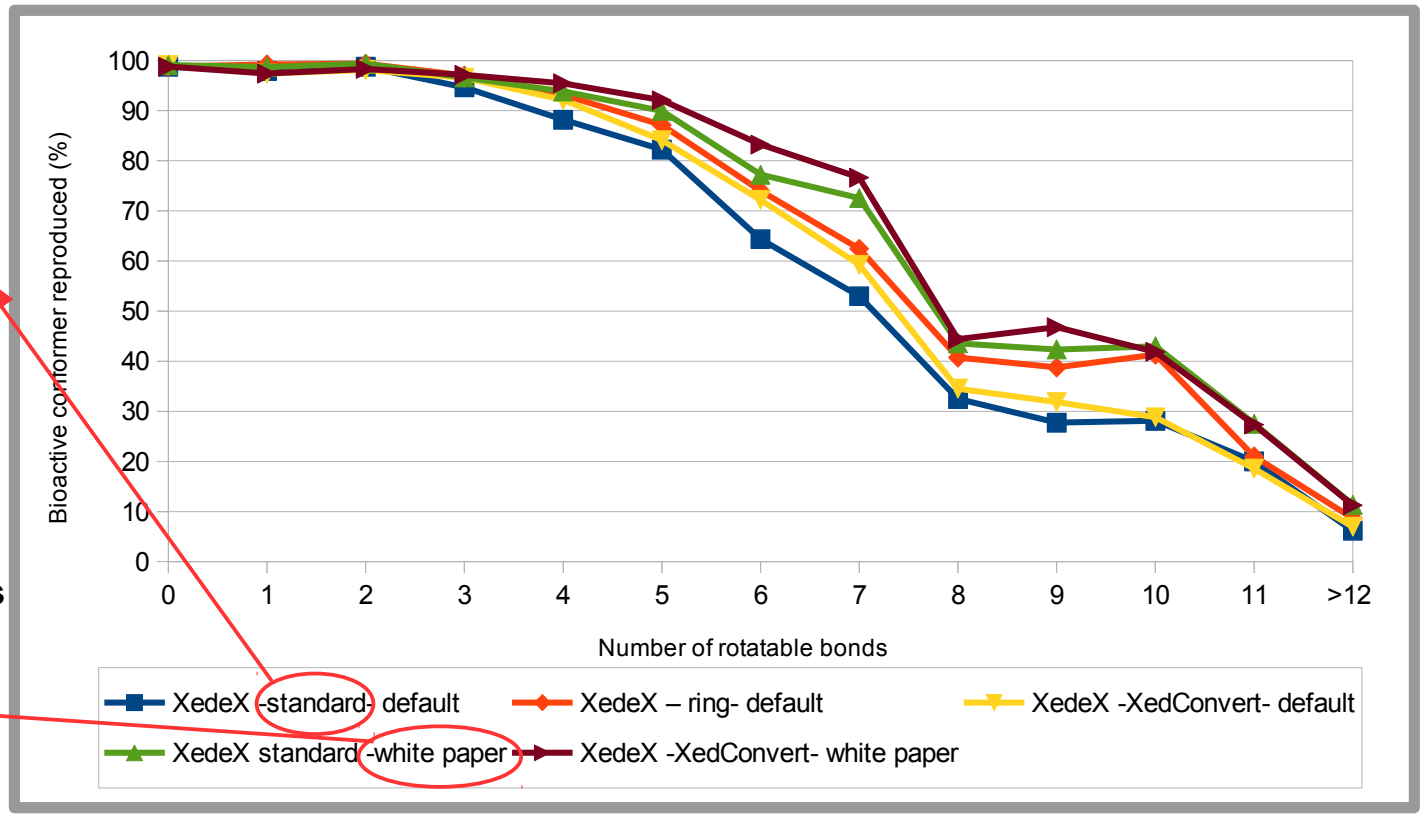
Pretreatments

Corina:
- Standard
- Ring conformations

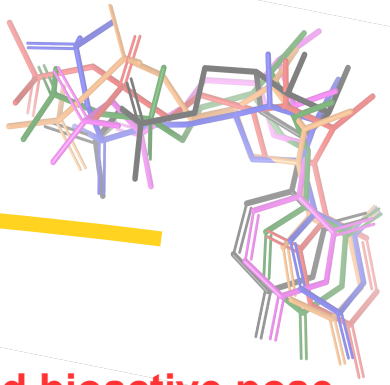
Xedconvert

Number of conformers

Default: 100
White paper: 300



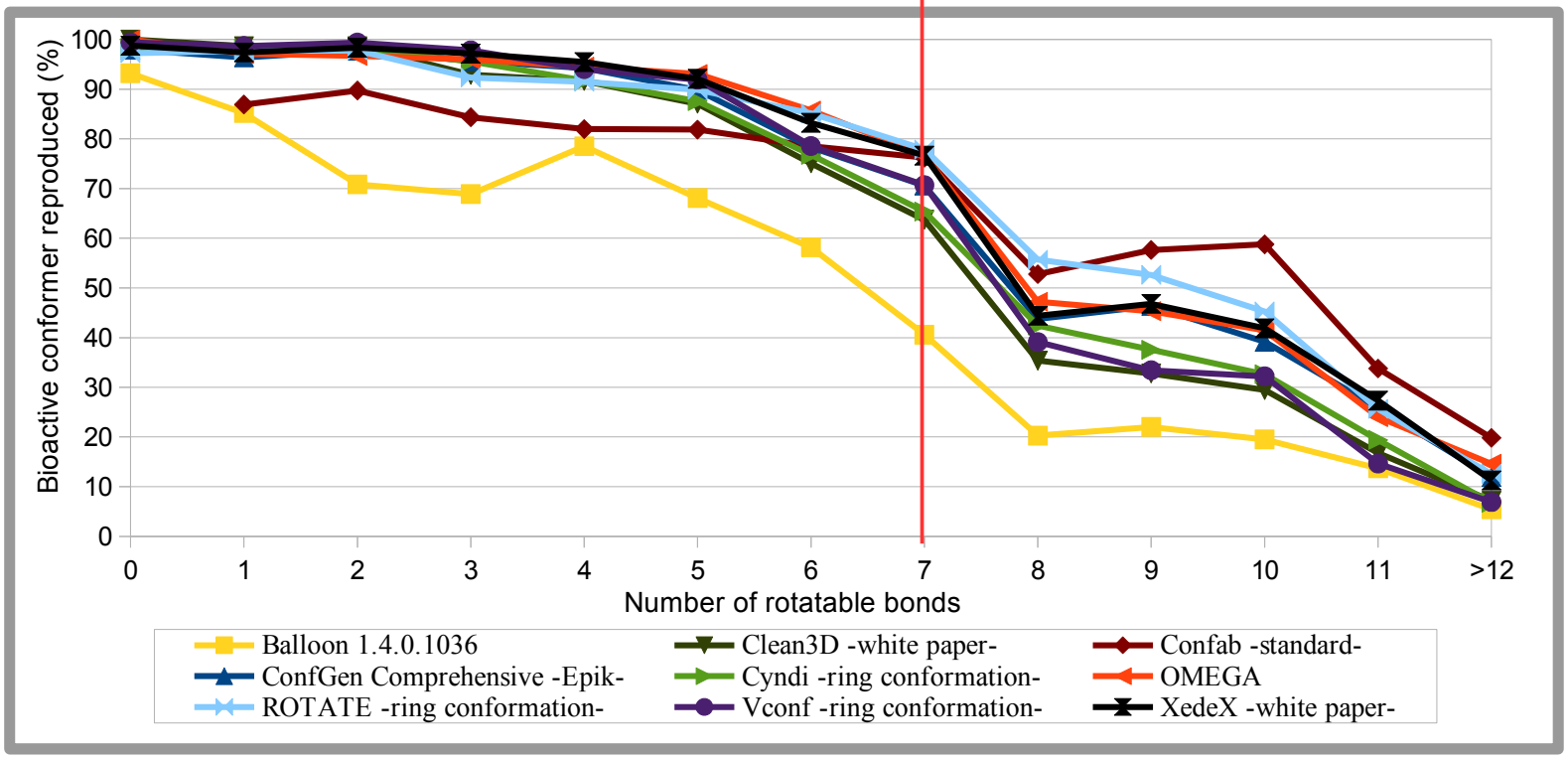
RESULTS



Success to reproduce the bioactive conformation

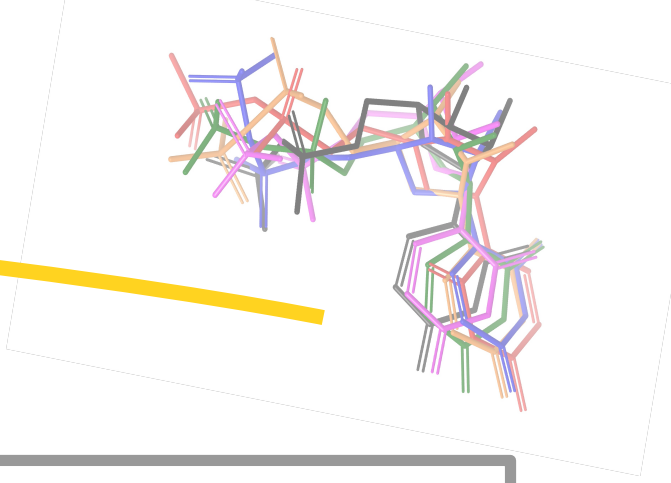
Cutoff of RMSD is 1 Å between active pose and a conformation

Reliability to find bioactive pose deacrease from seven rotatable bonds

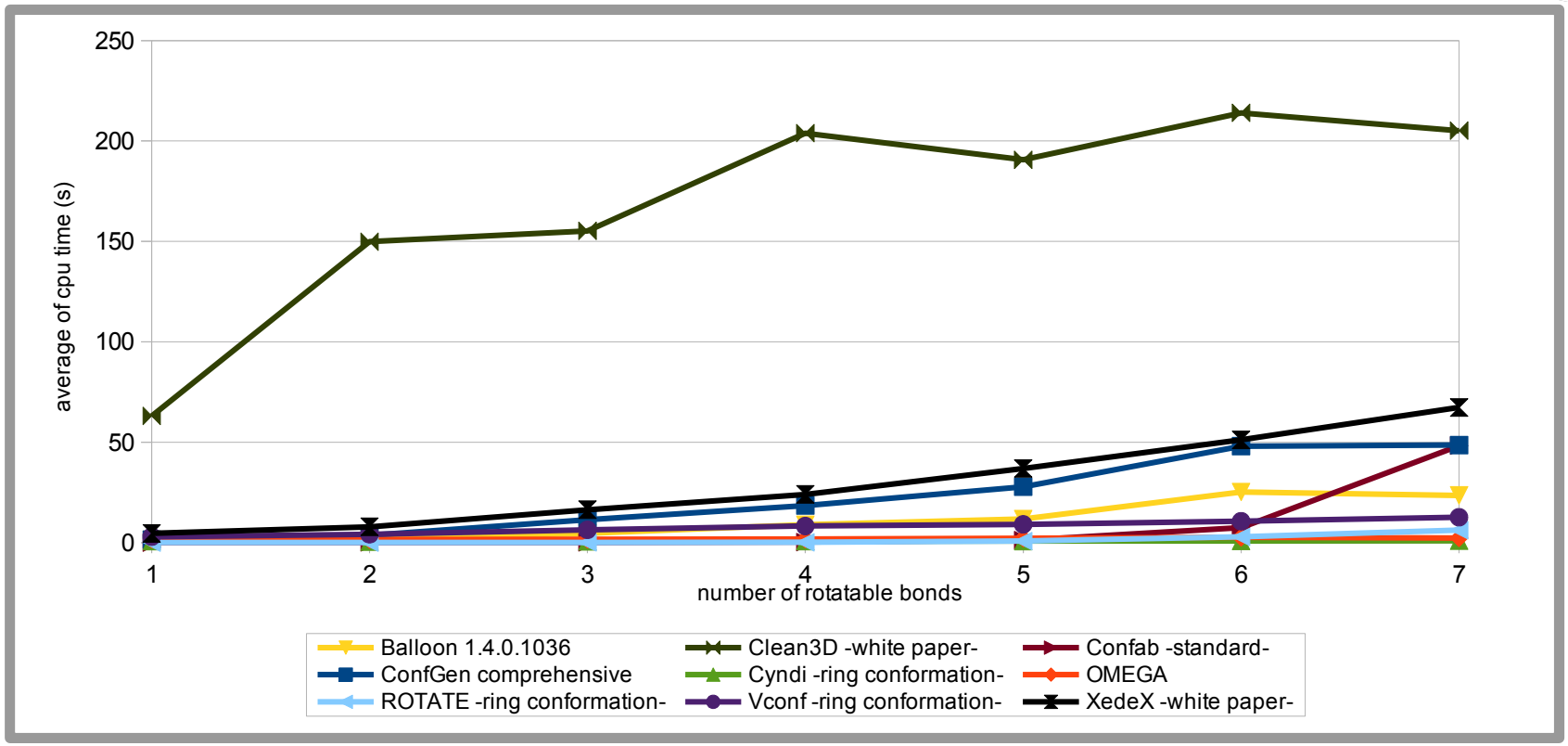


As increase the number of rotatable bonds, increase the difficult to reproduce bioactive pose

RESULTS



Amount of time to used to generate conformers per compound



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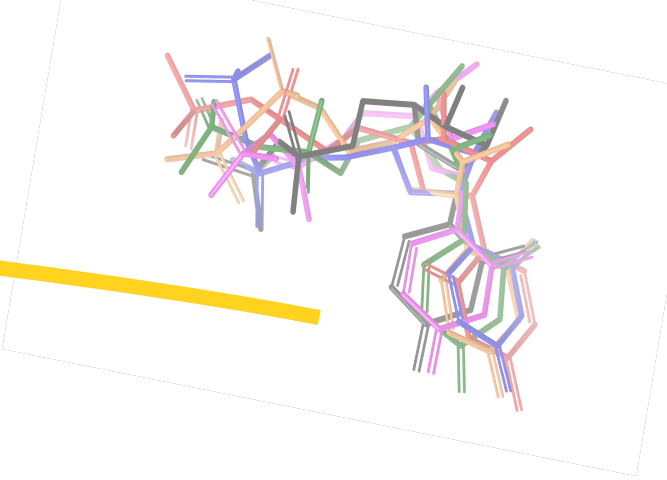
RESULTS



The average number of conformers generated per compound

↑ Number of conformers → ↑ Conformational space covered → Easier to find bioactive conformers

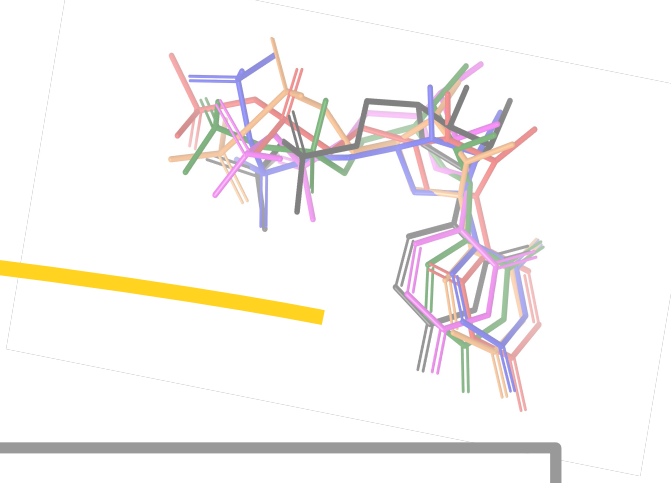
+

But ...

Noise into the system

↑ Number of false positives

RESULTS



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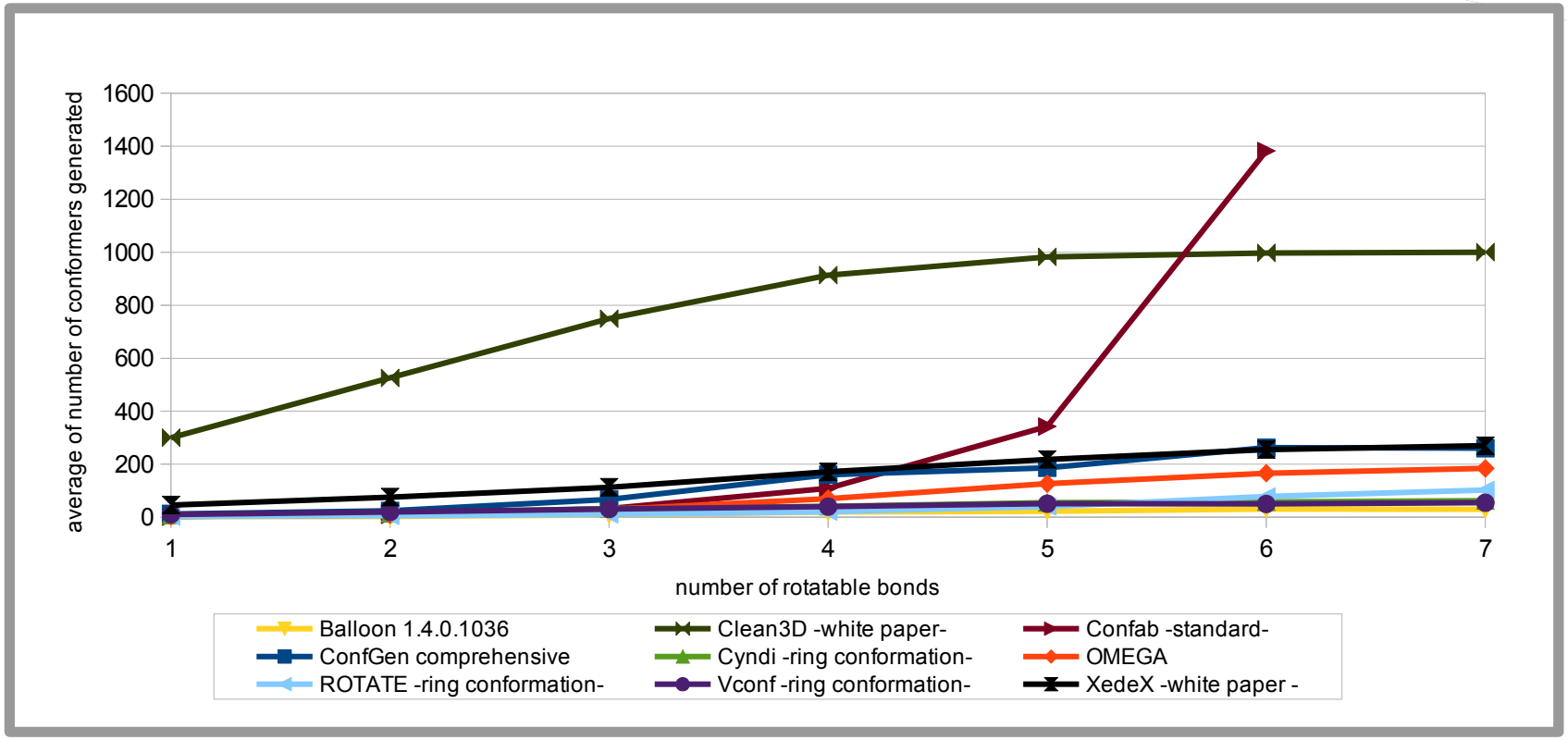
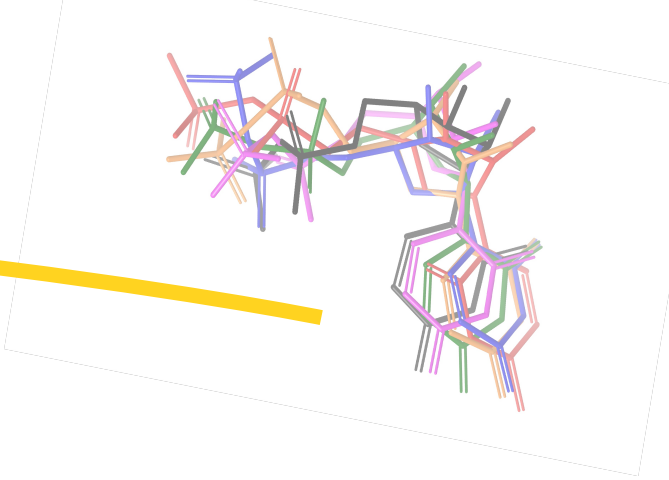
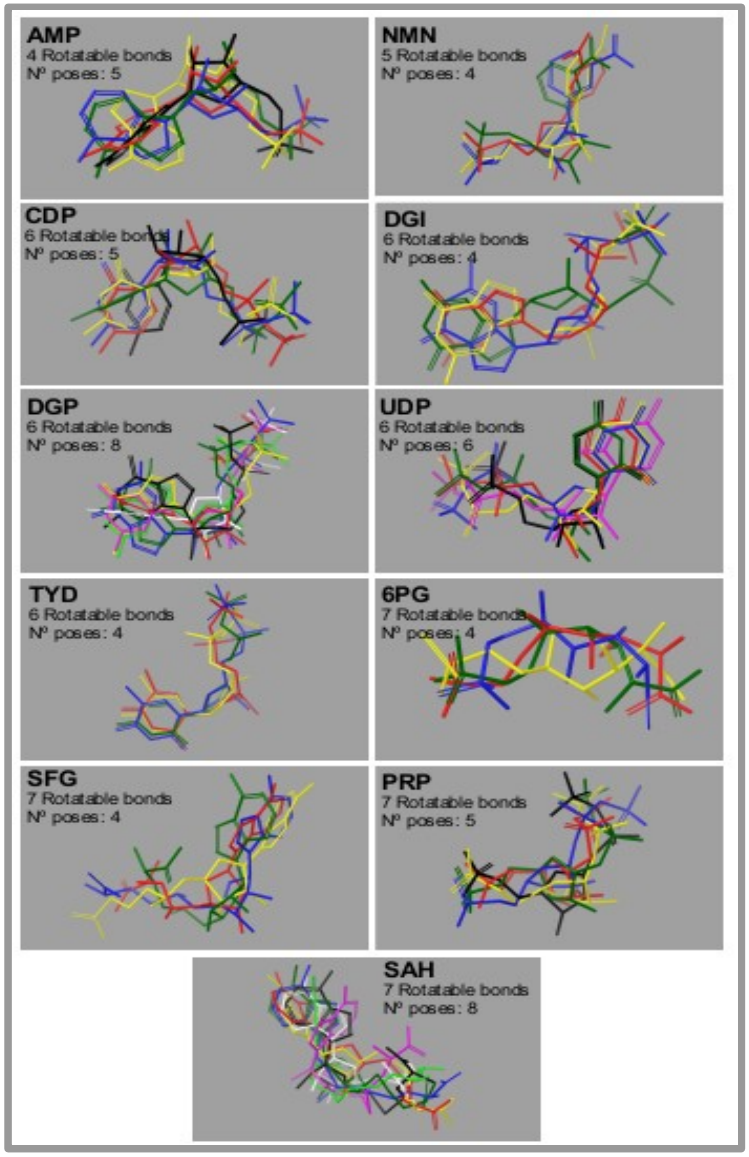


Maximum number of conformers by default is: a million for Confab; 300 for Cyndi; 200 for OMEGA; 100 number of searches for Vconf. In white papers, 1000 conformers have been generated for Clean3D; 300 for Balloon and 300 for XedeX. No upper limit exists for ROTATE and ConfGen

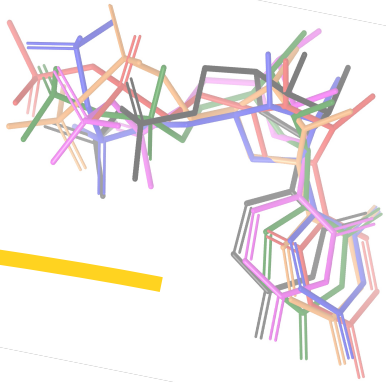
RESULTS



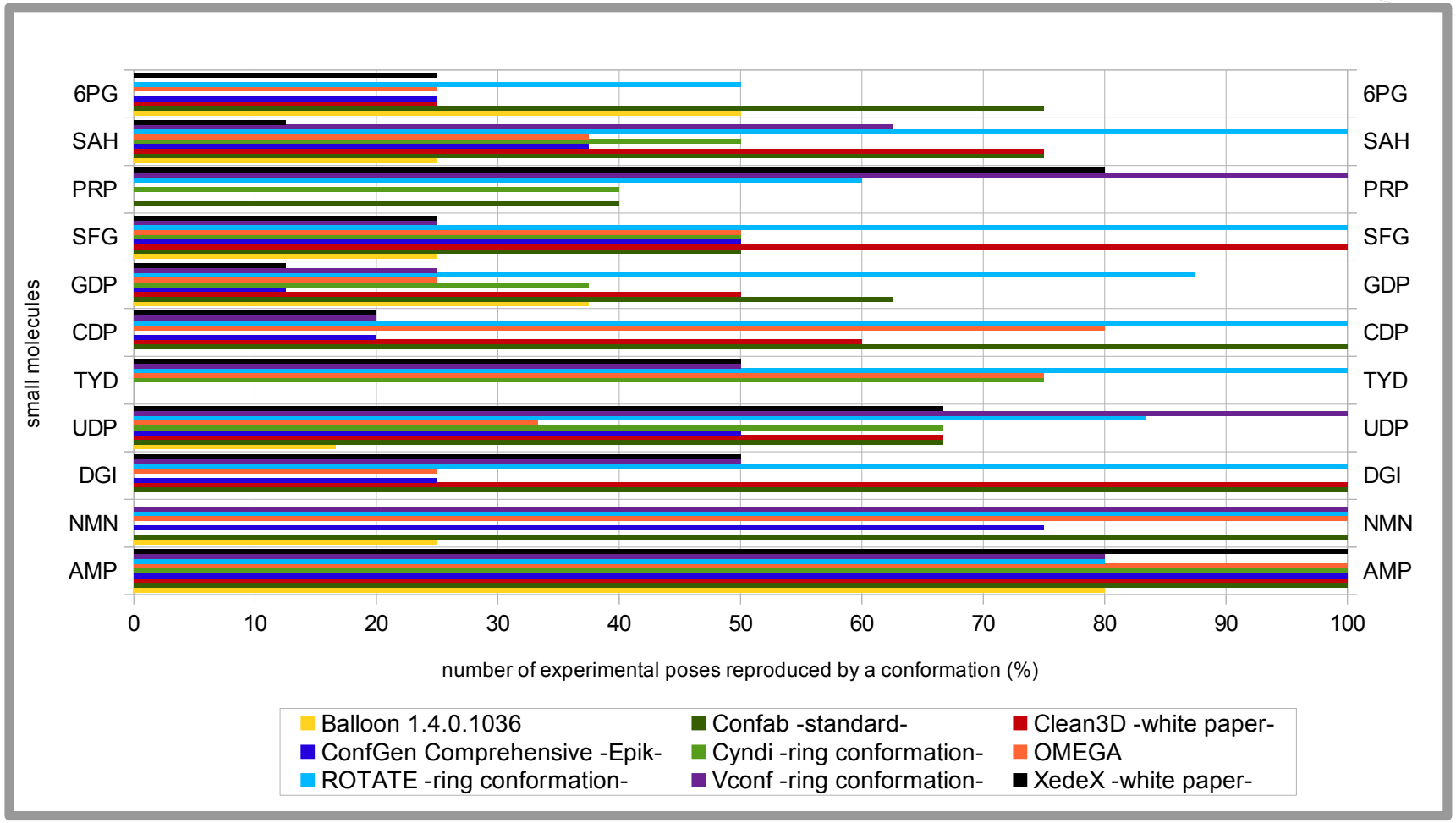


Ligands represented by more than four bioactive conformers that are significantly different (RMSD > 1.5 A)

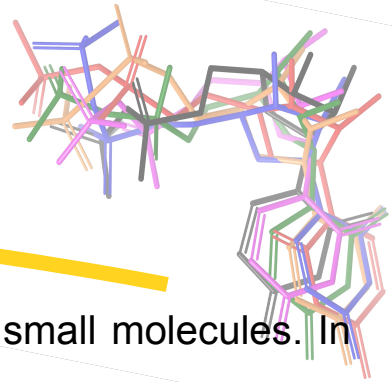
RESULTS



Reproduction of bioactive conformations that belong to the same ligand



CONCLUSIONS



➔ The reproduction of bioactive conformers depends on the flexibility of small molecules. In this way, until seven rotatable bonds the success is higher than 80%.

➔ OMEGA, ROTATE (with ring conformations) and XedeX have had more ability to generate conformers closer to bioactive conformer.

➔ The size of conformational ensamble is bigger for Clean3D and Confab (for more than six rotatable bonds). Therefore, it can increase the probability of obtaining bioactive structure, but also it can expect to introduce noise into the system.

➔ More active poses that belong to the same ligand are reproduced accurately by ROTATE (with ring conformations).

FUTURE PERSPECTIVE

➔ Proposal development of a database of pre-generated conformations of small molecules with less than seven rotatable bonds (70% of small molecules of Zinc Database) . It will allow to find bioactive conformers for a specific binding site of interest with a high probability to be the active one filtering by a pharmacophore.

ACKNOWLEDGEMENTS

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