In silico development of new acetylcholinesterase inhibitors

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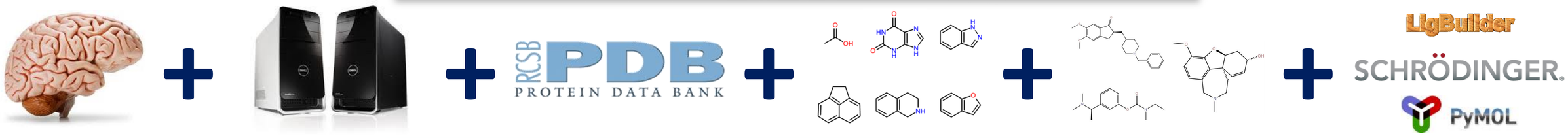
ABSTRACT

In this work we made use of the fragment-based drug design (FBDD) and de novo design to obtain more powerful acetylcholinesterase (AChe) inhibitors. The acetylcholinesterase is associated to the Alzheimer's Disease (AD). It was found that the cholinergic pathways in the cerebral cortex is compromised in AD and the accompanying cholinergic deficiency contributes to the cognitive deterioration of AD patients. In the FBDD approach, fragments are docked into the active site of the protein. As fragments are molecular groups with low number of atoms, it is possible to study they interaction with localized amino acids. Once the interactions are measured, the fragments are organized by affinity and then linked between them to form new molecules with high degree of interaction with the active site. In the other approach, we used the de novo design technique starting from reference drugs used in the AD treatment. These drugs were break into fragments (seeds). In the growing strategy, fragments were add to each seed growing new molecules. In the linking strategy, two or more separated seeds are linked with different fragments. Both strategies produced a library of more than 2M compounds. This library was filtered using ADME properties. The resulting library with around 6k compound was filtered again. In this case, structures with Tanimoto coefficient greater than 0.85 were discarded. The final library with 1.5k compounds was submitted to docking studies. As a result, 10 compounds with better interaction energy than the reference drugs were obtained.

MATERIALS



METHODS and RESULTS

1

PROTEIN DATA BANK
- ✓ Search for "*acetylcholinesterase*"
- ✓ Choose the organism
- ✓ Choose the better resolution structure

2

PROTEIN PREPARATION WIZARD & CAVITY
- ✓ Prepare protein (fix missing chains, add hydrogens, remove waters, etc.)
- ✓ Search for cavities
- ✓ Evaluate *druggability* of the cavities

3

FRAGMENT BASED DRUG DESIGN & *De novo* DESIGN
- ✓ Dock fragments (*Exploring*)
- ✓ Evaluate each fragment interactions
- ✓ Create "seeds" from reference drugs
- ✓ Grow new molecules (*growing*)
- ✓ Link fragments & seeds (*linking*)
- ✓ Build molecules (1st library: 2 500 000 molecules)

4

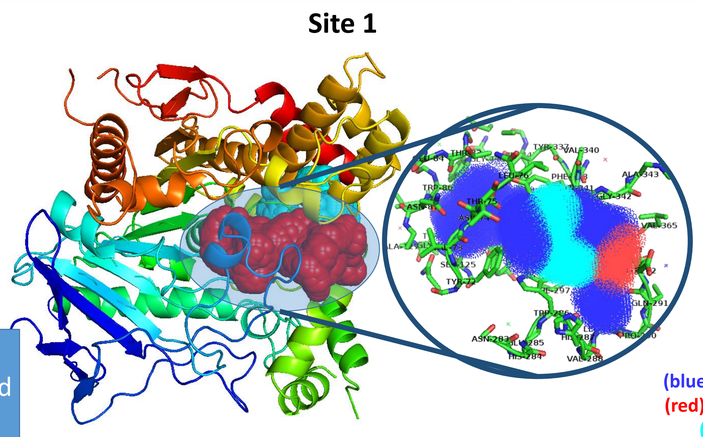
FILTERING & DOCKING
- ✓ Filtering by ADME properties (2nd library: 6k molecules)
- ✓ Filtering by Similarity using Tanimoto coefficient lower than 0.85 (3rd library: 1.5k molecules)
- ✓ 1st Screening: rigid-flexible docking (4th library: 100 molecules)

5

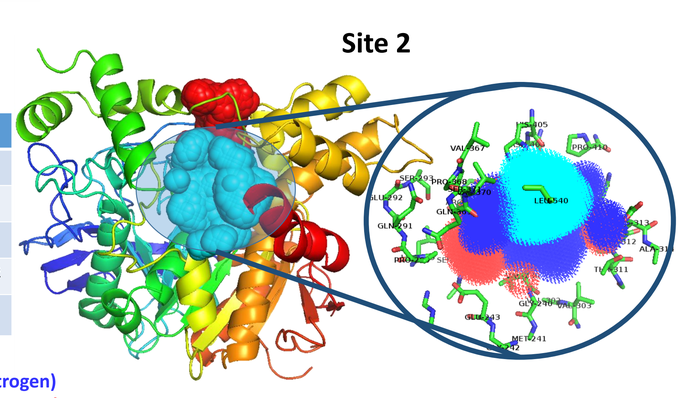
INDUCED FIT DOCKING (IFD)
- ✓ Flexible-flexible docking: reference drugs
- ✓ Flexible-flexible docking: 4th library
- ✓ Best 10 molecules

6

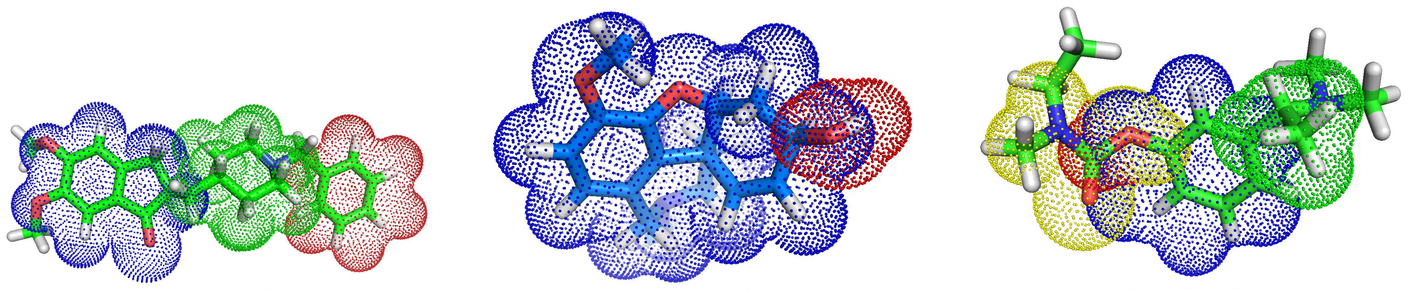
RESULTS
- ✓ Values for: van der Waals, lipophilic, Coulomb, hydrogen interaction energies
- ✓ Number of good, bad and ugly contacts
- ✓ 2D interaction diagrams: H-Bond, $\pi - \pi$ stacking, $\pi -$ cation.

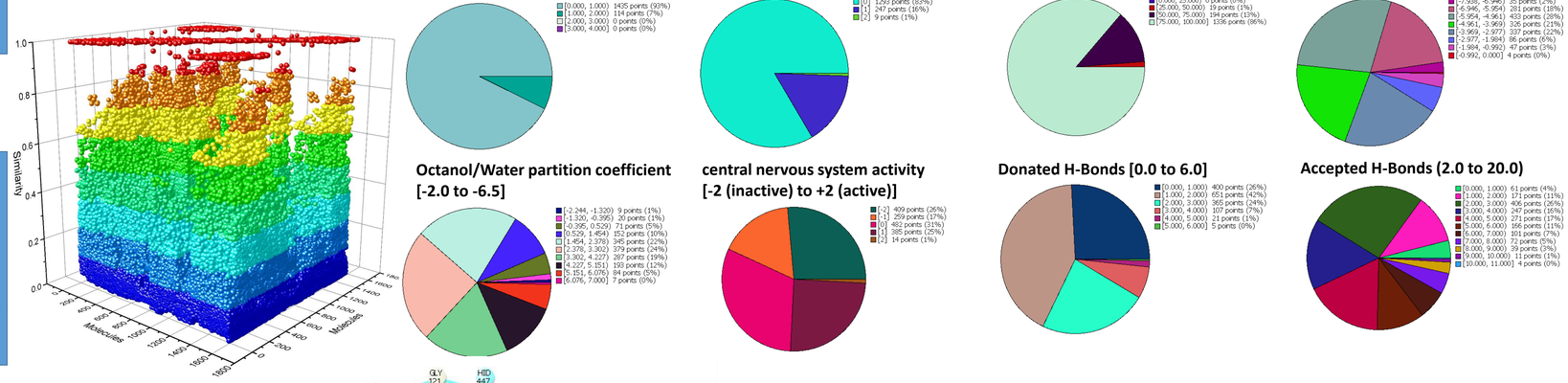


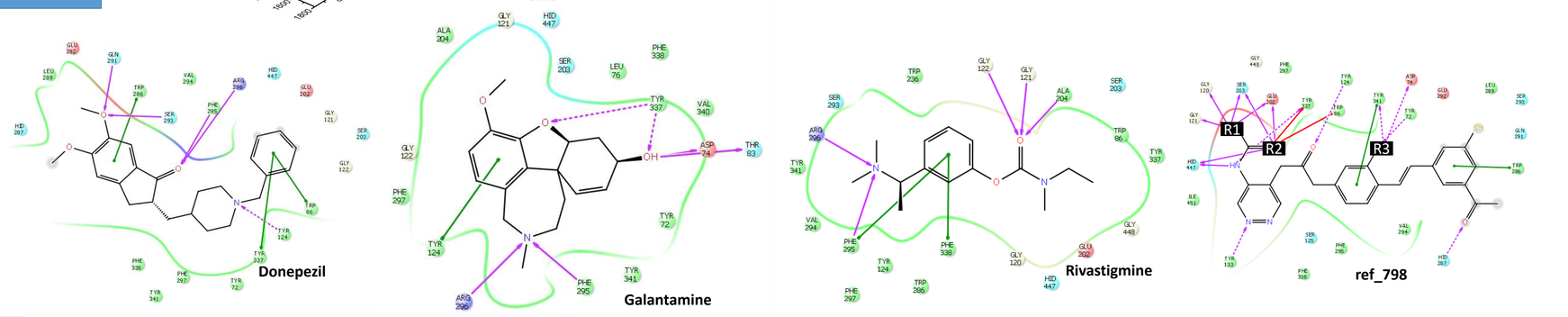
Site 1	Property	Site 2
11.18	*RankScore*	7.56
6.52	pKd	6.83
1320.00	*DrugScore*	-285.00
819.00 Å^2	Area	484.00 Å^2
+	*Druggability*	-



(blue) represent hydrogen-bond donor sites (nitrogen)
(red) represent hydrogen-bond acceptor sites (oxygen)
(green) represent hydrophobic sites (carbons)







Molecule	GScore*	E_{lipo}	E_{HBond}	E_{vdW}	E_{Coul}
798	**-17.352**	**-1.928**	**-0.856**	**-49.224**	**-26.696**
746	**-17.043**	**-2.021**	**-0.480**	**-53.265**	**-14.981**
671	**-16.192**	**-1.133**	**-0.658**	**-40.011**	**-17.199**
Donepezil	**-11.676**	**-2.082**	**-0.242**	**-43.891**	**-6.114**
Galantamine	**-12.074**	**-1.045**	**-0.200**	**-30.595**	**-14.030**
Rivastigmine	**-8.437**	**-0.685**	**-0.423**	**-34.487**	**-6.767**

* All values are in kcal/mol

- ✓ CAVITY: Curr. Pharm. Des. **19**, 2326 (2013); Y. Yuan, J. Pei e L. Lai
- ✓ LigBuilder: J. Chem. Inf. Model. **51**, 1083 (2011); Y. Yuan, J. Pei e L. Lai
- ✓ Similarity: J. Med. Chem. **57**, 3186 (2014); G. Maggiora, M. Vogt, D. Stumpfe e J. Bajorath
- ✓ ADME: QikProp, version 3.2, Schrödinger, LLC, New York, NY, 2009.
- ✓ *Docking*: J. Med. Chem. **49**, 6177 (2006); R.A. Friesner, *et al.*
- ✓ *Induced Fit Docking*: J. Med. Chem. **49**, 534 (2006); W. Sherman, *et al.*

CONCLUSIONS

- The protein cavities were scanned and classified.
- A first library with 2 500 000 molecules was obtained.
- A second library with ~6000 molecules was obtained from 1st library after filtering by ADME properties.
- A third library with ~1500 molecules was obtain filtering the 2nd library using similarity.
- Rigid-flexible docking studies were carry with the 3rd library. The best 100 molecules were used in flexible-flexible docking together with the reference drugs.

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