# De Novo Drug Design for Alzheimer's Disease

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# Contents

## Abstract

Alzheimer’s disease (AD) affects approximately 10% of the world’s population with 65 years of age, being the most common form of dementia and is characterized by senile plaquets and cholinergic deficits. Currently, however, only a handful of drugs are available and they are at best only able to offer some relief of symptoms. In this work, we are aimed to take the recently popular drug, donepezil, as framework to design novel effective drugs for the treatment of AD. In this proposal, we will also recommend a well-known suite of software named “Discovery Studio”, which is developed by Accelrys. We will give a brief introduction about how we apply such a software in our study and, generally, in CADD. By using this powerful tool, modeling, scoring, designing, evaluation and ADMET can be conducted to help us achieve *de novo* drug design for AD.

**Key Words:** Alzheimer’s disease (AD), *de novo* drug design, Accelrys, Discovery Studio, donepezil, AChEI.

# 1. INTRODUCTION

### 1.1 Alzheimer’s Disease

Alzheimer's disease whose medical literature is Alzheimer disease (AD), is the most common form of dementia. This disease was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him. Up to now, it seems that there is no cure for the disease. It worsens as progressing, and can eventually lead to death. Most often, AD affects approximately 10% of the world’s population with over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier.

Although Alzheimer's disease develops quite differently for every individual, there are still many common symptoms.

In the early stages, difficulty in remembering recent events appears frequently on patients (however, these symptoms are often mistakenly regarded as 'age-related' concerns, or manifestations of stress).

As the disease advances, symptoms can include confusion, irritability, aggression, mood swings, trouble with language, and long-term memory loss. As the sufferer declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death. On average, the life expectancy following diagnosis is approximately seven years. Fewer than three percent of individuals live more than fourteen years after diagnosis.

As of 2012, more than 1000 clinical trials have been or are being conducted to test various compounds in AD. Because AD cannot be cured and is degenerative, the sufferer relies on others for assistance. The role of the main caregiver is often taken by the spouse or a close relative. Alzheimer's disease is known for placing a great burden

on caregivers; the pressures can be wide-ranging, involving social, psychological, physical, and economic elements of the caregiver's life. In many developed countries, AD is one of the most costly diseases to society.

### 1.2 Cause and Hypothesis

The cause for most Alzheimer's cases is still mostly unknown except for few cases where genetic differences have been identified. Several competing hypotheses exist trying to explain the cause of the disease:

The cholinergic hypothesis, on which most currently available drug therapies are based, proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine.

The amyloid hypothesis postulated that extracellular beta-amyloid (Aβ) deposits are the fundamental cause of the disease. This hypothesis traditionally points to the accumulation of beta-amyloid peptides as the central event triggering neuron degeneration.

The tau hypothesis is the idea that tau protein abnormalities initiate the disease cascade. In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies and the microtubules disintegrate, collapsing the neuron's transport system.

Also, there are many other hypothesis, but most of them are not popular and didn't lead to any effective drugs and treatments.

### 1.3 Medical Therapy

Since the cause and progression of Alzheimer's disease are not well understood, current treatments can only help with the symptoms of the disease. There are no available treatments that stop or reverse the progression of the disease. A handle of drugs for the disease can only deal with the symptoms. There are two kinds of medicine usually used to offer relief of the symptoms:

First category is acetylcholinesterase inhibitors, which includes tacrine, rivastigmine, galantamine and donepezil. Acetylcholinesterase inhibitor (often abbreviated AChEI) or anti-cholinesterase is a chemical that inhibits the acetylcholinesterase enzyme from breaking down acetylcholine, thereby increasing both the level and duration of action of the neurotransmitter acetylcholine. Reversible, quasi-irreversible (or pseudirreversible in some sources) and irreversible inhibitors exist.

The other one is memantine. This drug belongs to a class of drugs called NMDA receptor antagonists, which reduce certain types of brain activity by binding to NMDA receptors on brain cells and blocking the activity of the neurotransmitter glutamate. At normal levels, glutamate aids in memory and learning, but if levels are too high, glutamate appears to overstimulate nerve cells, killing them through excitotoxicity.

### 1.4 Our Targets

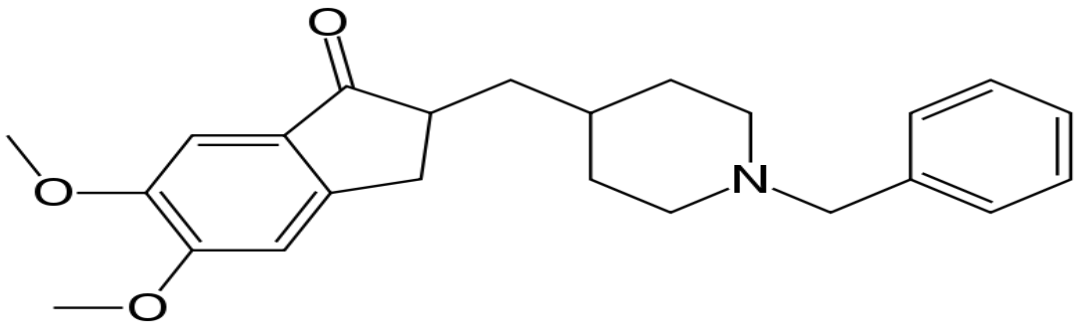
Recent data have shown that donepezil, which is one of the AChEI, has a stronger effect on AD, compared with other kinds of drugs. However, we found that this "most effective" treatment seemed not the best way because its docking score, given by reference 2, shows that there are still a lot of work that can be done to improve this drug.

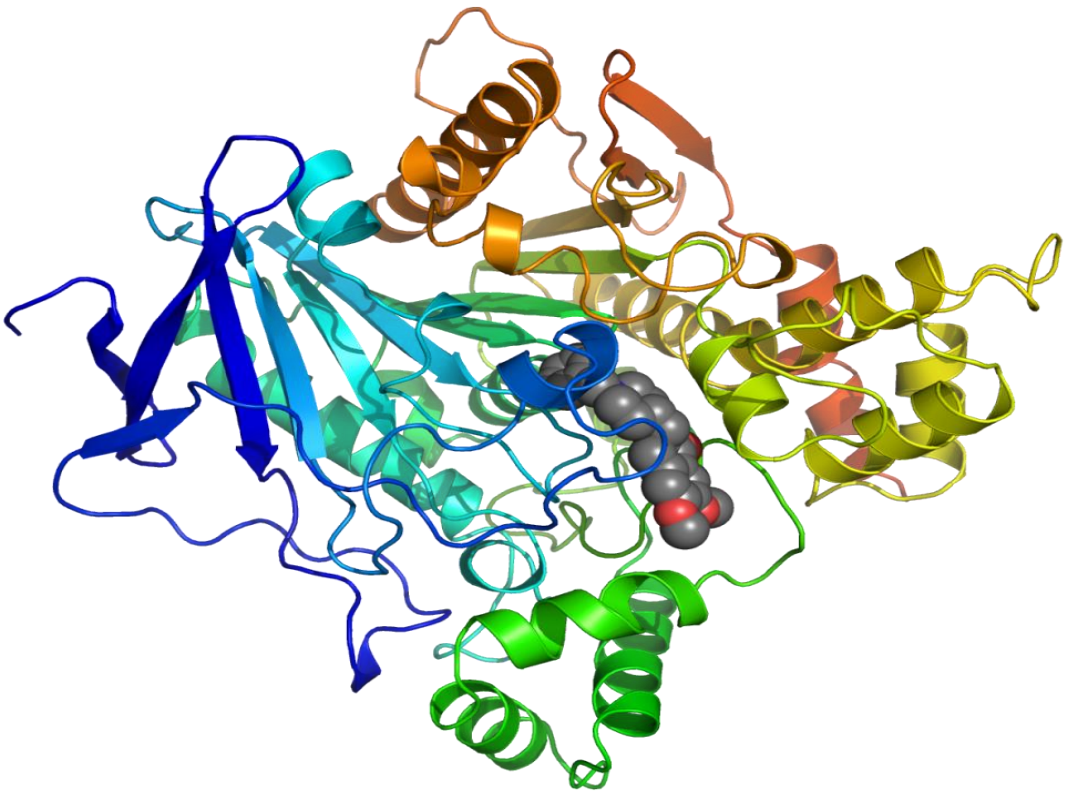
So in this proposal, we want to use a recommended software, named Discovery Studio, to design a new type of "donepezil", based on its original structure and function region.

## 2. MATERIALS AND METHODS

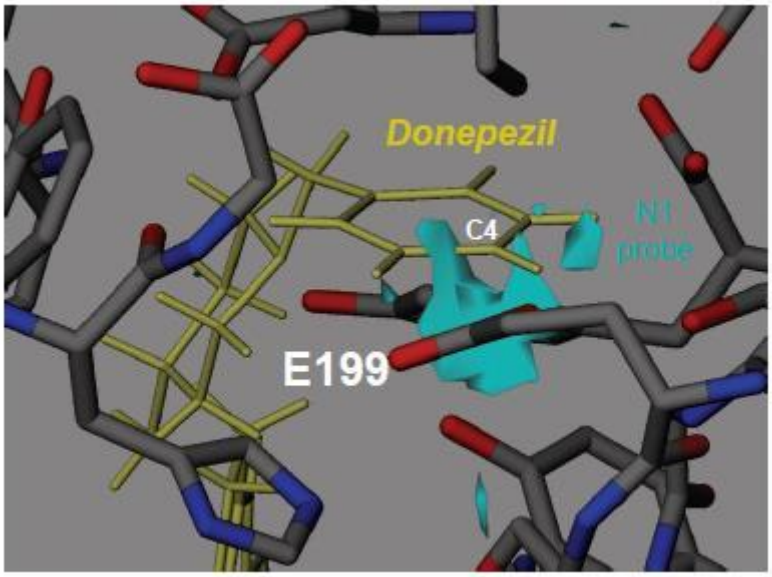
### 2.1 Donepezil

Donepezil is a drug named after DONEP by Alkem Pentacare, which is the company that first developed this drug. Its main component is a centrally acting reversible acetylcholinesterase inhibitor. The therapeutic use of donepezil is in the palliative treatment of Alzheimer's disease. Common side effects include gastrointestinal upset. It has an oral bioavailability of 100% and easily crosses the blood–brain barrier. Because it has a biological half-life of about 70 hours, it can be taken once a day. The molecular structure and three-dimensional structure from PDB are following:



And its function model is like following:




Our study and work are based on this molecule. It is the foundation of our *de novo* design.

## 2.2 Accelrys Software

Accelrys is a software company headquartered in the United States, with representation in Europe and Asia. It provides software for chemical, materials and bioscience research for the pharmaceutical, biotechnology, consumer packaged goods, aerospace, energy and chemical industries. It is a company that specializes in scientific software products covering computational chemistry, computational biology, cheminformatics, molecular simulations and Quantum Mechanics. For example, "The Accelrys Enterprise Platform", a scientifically software for enterprise lab management, modeling and simulation, or workflow automation. "Pipeline Pilot", a program that aggregates and provides immediate access to the volumes of disparate research data locked in silos. "Symyx Notebook", an Electronic lab notebook, "Discovery Studio", a suite of modeling and simulation programs for life sciences, and so on. Among the various kinds of highly-recommended software, "Discovery Studio" is the one that will play an important role in our work.

## 2.3 Discovery Studio

Built on the Accelrys Enterprise Platform and Pipeline Pilot visual programming product, Discovery Studio is a well-known suite of software for simulating small molecule and macromolecule systems.

Discovery Studio is typically used in the development of novel therapeutic medicines, including small-molecule drugs, therapeutic antibodies, vaccines, synthetic enzymes, and even in areas such as consumer products. It is used regularly in a range of academic and commercial entities, but is most relevant to Pharmaceutical, Biotech, and consumer goods industries. Much more

introduction about Discovery Studio can be accessed on following website: http://accelrys.com/products/discovery-studio/ .
Discovery Studio is a client-server software suite, which can be run on both Windows and Linux systems. The product suite includes both paid-for licensed versions and free visualization client tools. For our study, the free version is certainly the choice. The download website is: http://accelrys.com/products/discovery-studio/visualization-download.php (you can also find tutorial and manual there).
The latest version is 3.5, and 4.0 is coming soon, according to the official announcement. If you want to download it, all you need to do is filling a form and submitting it. Then you can get your own Discovery Studio. It is a powerful tool for computational chemistry and biology, and perform as well as MOE in de novo drug design, as the comments from internet.
Concluded from Wiki, Discovery Studio provides software applications covering the following areas:

a) Simulations (Including Molecular Mechanics, Molecular Dynamics, Quantum Mechanics, hybrid QM/MM calculations and so on);
b) Ligand Design (Including tools for enumerating molecular libraries and library optimization);
c) Pharmacophore modeling (Including creation, validation and virtual screening);
d) Structure-based Design (Including tools for fragment-based placement and refinement, receptor-ligand docking and pose refinement, de novo design);
e) Macromolecule design and validation;
f) Macromolecule engineering;
g) Specialist tools for protein-protein docking;
h) Specialist tools for Antibody design and optimization;
i) Specialist tools for membrane-bound proteins, including GPCRs;
j) QSAR (Covering methods such as multiple linear regression, partial least squares, recursive partitioning, Genetic Function approximation and 3D field-based QSAR);
k) ADME;
l) Predictive toxicity.

What we are going to use in our design, among all the functions mentioned above, are simulations, pharmacophore modeling, QSAR, de novo evolution, ADME and predictive toxicity.

## 2.4 Methods

Our protocol consists of four steps to achieve the new drug design:

a) Homology Modeling:
   To build homology modeling, we first should get the amino acid sequence (target receptors, AChE) from NCBI or GeneBank and protein structure (also target protein, AChE) from PDB. Then we construct an atomic-resolution

model of the target protein from its amino acid sequence and an experimental three-dimensional structure of a related homologous protein by using the simulations function in Discovery Studio. This work may rely on the identification of one or more known protein structures likely to resemble the structure of the query sequence. The target structure is produced from the known sequence alignment and the template structure and its sequence. Detectable levels of sequence similarity usually imply significant structural similarity due to the high conservation of protein structures.

b) Docking and Scoring:
According to the reference papers, DockScore, PLP1, PLP2 and PMF, the four main score functions in the Discovery Studio, may be the best choice to achieve docking. Candidate ligand poses were evaluated and prioritized according to the DockScore function. There are two types of DockScore in the software. One is based on a force-field approximation, the other on the piecewise linear potential function (PLP).

Equation 1: DockScore (forcefield) = - (ligand/receptor interaction energy + ligand internal energy)

Equation 2: DockScore (PLP) = - (PLP potential)

P.S. 1: In Equation 1, the interaction energy is taken as the sum of the van der Waals energy and electrostatic energy, and the internal energy of the ligand is computed when using the force-field version of DockScore (the purpose of including the internal energy is to avoid ligand conformations with bad internal nonbond clashes. By default, only the standard (not softened) van der Waals energy is used for the ligand internal energy.
P.S. 2: The PLP version of DockScore uses both PLP1 and PLP2 function. In the PLP1 score function, there are four atom types as following:
i) Hydrogen bond donor only;
ii) Hydrogen bond acceptor only;
iii) Both hydrogen bond donor and acceptor;
iv) Non-polar.
In the PLP2 score function, the atom typing remains the same as in the PLP1 score function. In addition, an atomic radius is assigned to each atom expected for hydrogen.The score function of DockScore is the default function in the Discovery Studio.

c) *De novo* Evolution:
To design the new compounds from the potent drugs, we should use the program "*De novo* evolution in the Discovery Studio, a function especially for getting new compounds. Take donepezil as the template and set the parameters we get above and from references, then we can have several candidates for the new drug. We will take them into the protein acceptor binding pocket and

compare the scores.

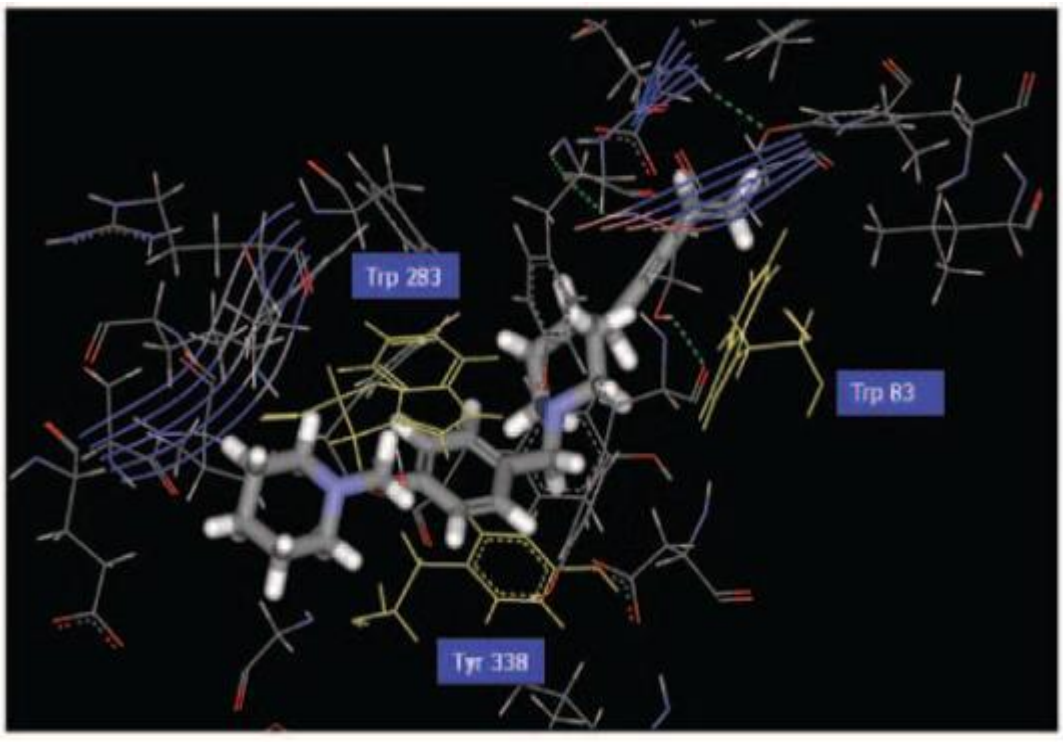
d) ADMET:
Adsorption, Distribution, Metabolism, Excretion and Toxicity analysis will be done for testing and evaluating traditional drug, donepezil, and our new AChE inhibitors by using the relative function in Discovery Studio. We carry out this step to estimate the following properties: aqueous solubility blood-brain barrier penetration (BBB), cytochrome P450 (CYP450) 2D6 inhibition, hepatotoxicity human intestinal absorption (HIA) and plasma protein binding. Furthermore, key issue was to calculate the BBB and other factors as the drugs should pass through the BBB to react with the receptor protein to cure AD. Comparison of the two set of scores can tell us whether the new drugs we develop are better or worse than their template: donepezil, and how we should improve to get an expected product.

# 3. EXPECTATION AND DISCUSSION

## 3.1 Expected Results

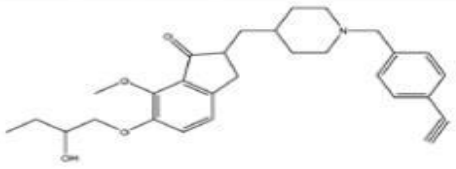
The following tables or figures should appear in our work (these pictures are mainly from reference 2 ):

**Modeling:**

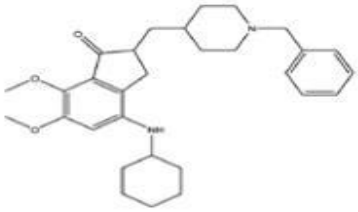


**Docking and Scoring:**

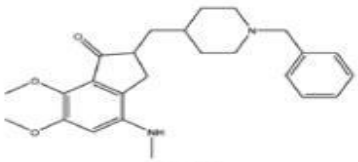
Table I. Score values of new AChE inhibitors and donepezil.



Evo27

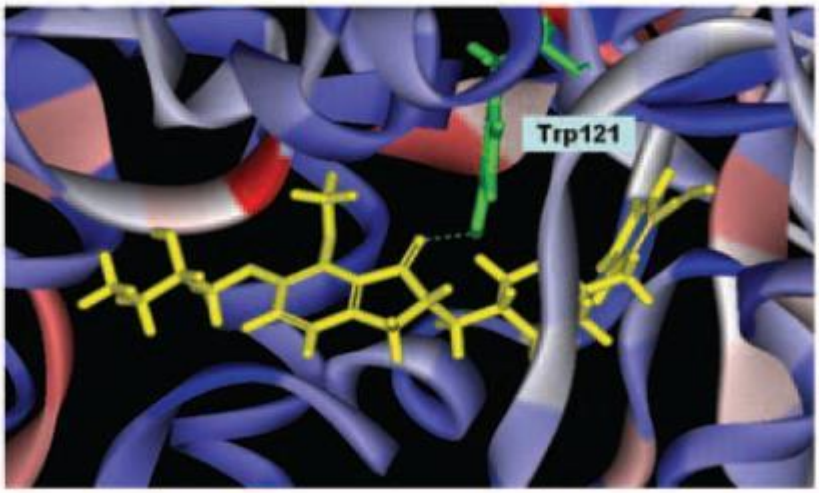


Evo9



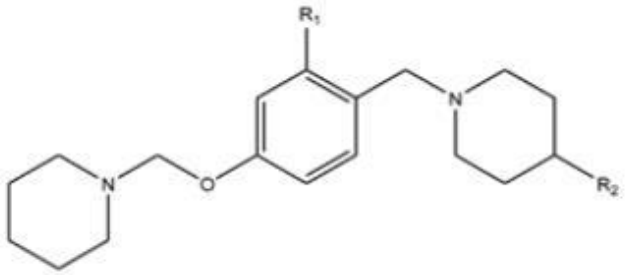
Evo10

| | -PLP1 | -PMF | DockScore |
|---|---|---|---|
| Donepezil | 78.52 | 153.85 | 67.85 |
| Evo27 | 99.07 | 163.26 | 81.39 |
| Evo9 | 105.72 | 197.40 | 79.89 |
| Evo10 | 75.11 | 152.83 | 69.89 |



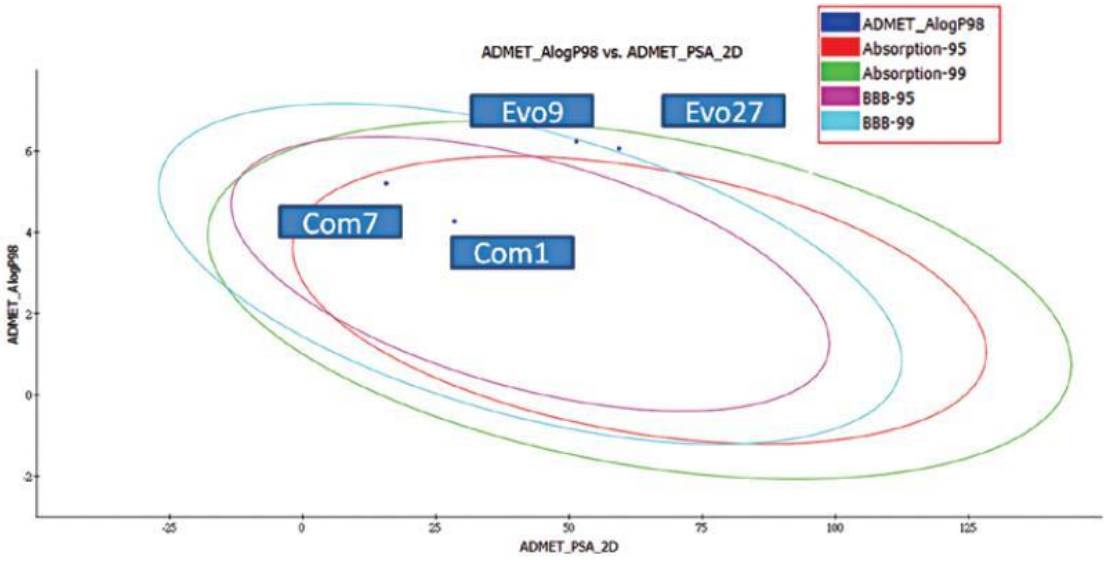
***De novo* Evolution:**

Table II. Score values of new dual inhibitors and donepezil.



| | R1 | R2 | -PLP1 | -PMF | DockScore |
|---|---|---|---|---|---|
| Com1 |  |  | 92.50 | 151.86 | 67.18 |
| Com7 |  |  | 79.08 | 136.39 | 67.08 |
| Com8 |  |  | 102.83 | 176.54 | 64.75 |
| Com2 |  |  | 73.73 | 145.28 | 64.57 |
| Donepezil | - | - | 78.52 | 153.85 | 67.58 |

**ADMET:**



### 3.2 Conclusion and Discussion

In order to develop novel effective drugs for the treatment of AD, in this study, we use homology modeling to simulate the characters of AChE. We used donepezil as a framework to detect whether more effective chemical compounds with better binding affinity exist. Our expected results may give a compound with the highest DockScore, which means it has stronger interactions with AChE. It will be a more effective drug for AD than donepezil. Furthermore, the docking studies may provide rational evidence that those inhibitors interact with target proteins, which offer additional direction to design more potent drugs for the treatment of AD.

Although this is just a proposal of what we want to do, but several latest papers about CADD have turned out that the protocol we described above is a popular and effective way for *de novo* drug design, and reference 2 used the same pipeline (but different base) to find a new drug for AD successfully. So we believe that our work will be of great significance if the studies can be carried out and our expectations are realized.

## 4. REFERENCE


1) Wikipedia;
2) Accelrys official website;
3) Chen PY, Tsai CT, Ou CY, Hsu WT, Jhuo MD, Wu CH, Shih TC, Cheng TH, Chung JG: *Computational analysis of novel drugs designed for use as acetylcholinesterase inhibitors and histamine H3 receptor antagonists for Alzheimer's disease by docking, scoring and de novo evolution.* MOLECULAR MEDICINE REPORTS 5: 1043-1048, 2012;
4) GREGORY N. TEW, RICHARD W. SCOTT, MICHAEL L. KLEIN, AND WILLIAM F. DEGRADO: *De Novo Design of Antimicrobial Polymers, Foldamers, and Small Molecules: From Discovery to Practical Applications.* ACCOUNTS OF CHEMICAL RESEARCH 30-39 January 2010 Vol. 43, No. 1;
5) Carlos H. T. P. da Silva, Ivone Carvalho & C. A. Taft:*Virtual Screening, Molecular Interaction Field, Molecular Dynamics, Docking, Density Functional, and ADMET Properties of Novel AChE Inhibitors in Alzheimer's Disease.* Journal of Biomolecular Structure and Dynamics, 24:6, 515-523.