# Case study: Pharmaceutical

## Development and screening of NMDA agonist

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Customer type

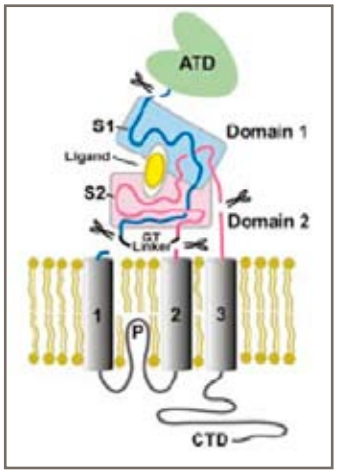
**A drug discovery company**

Software modules

**BioPredicta**

**MolSign**

**VLife Engine**




NR1 subunit

Application

**Lead optimization**

Techniques

**Protein structure analysis**

**Protein - ligand docking**

**Binding energy analysis**

### Background:

N-methyl-D-aspartate (NMDA) receptors are involved in activity dependent synaptic plasticity as well as in memory and learning. These receptors are also involved in several diseases and injuries including schizophrenia and excitotoxicity.

NMDA receptors require both glycine and glutamate, which bind to NR1 and NR2 domains respectively, for activation.

### Design challenge:

NMDA receptors are in 'open' conformation in their apo state. Suitable ligand binding in the NR1 domain causes closure of the cleft thereby allowing passage of $Ca^{2+}$ ions.

The degree of this closure and consequent activation depends on whether the ligand binding at NR1 domain is an agonist, partial agonist or antagonist.

The mandate given by the customer was to prioritize customer suggested molecules for NMDA agonist activity and suggest new compounds that can fit the agonist-binding site.

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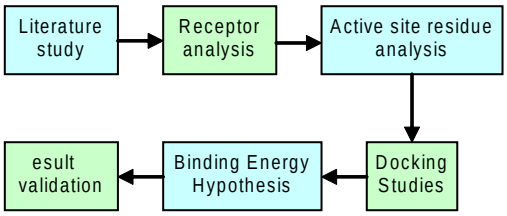
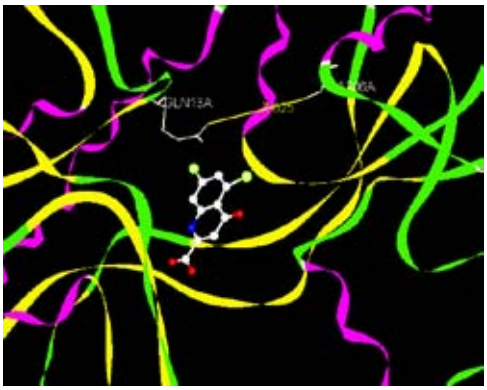



Workflow of project


Pic. A




Pic. B

## Project work:

The NMDA PDB structure was cleaned and was used for docking of customer compounds in place of the substrate. The binding energies as well as mode of binding of compounds were compared with standard molecules.

## Result analysis:

Distance between Gln13 and Ala206 was considered as measure of the cleft closure. The agonists showed this distance to be 3.83 Å, whereas it was 7.03Å when antagonist was bound to NMDA. All compounds were docked and ranked according to their ability to close the cleft.

Picture A shows interatomic distance (3.836Å) between the sidechain nitrogen of GLN13 and the side chain carbon atom of ALA206 in NMDA-D Serine (agonist) complex.

Picture B shows Interatomic distance (7.025Å) between the sidechain nitrogen of GLN13 and the side chain carbon atom of ALA206 in NMDA-DCKA (antagonist) complex.

WORLD INTELLECTUAL PROPERTY ORGANIZATION

Compositions for Enhancing Memory And Methods (Wo/2006/034196)

Our customer filed a patent related to the discovery work done by VLife

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