# Identification of selective inhibitors against BACE 1 over BACE 2 in Alzheimer's disease by Quantitative Structure-Activity Relationship (QSAR)

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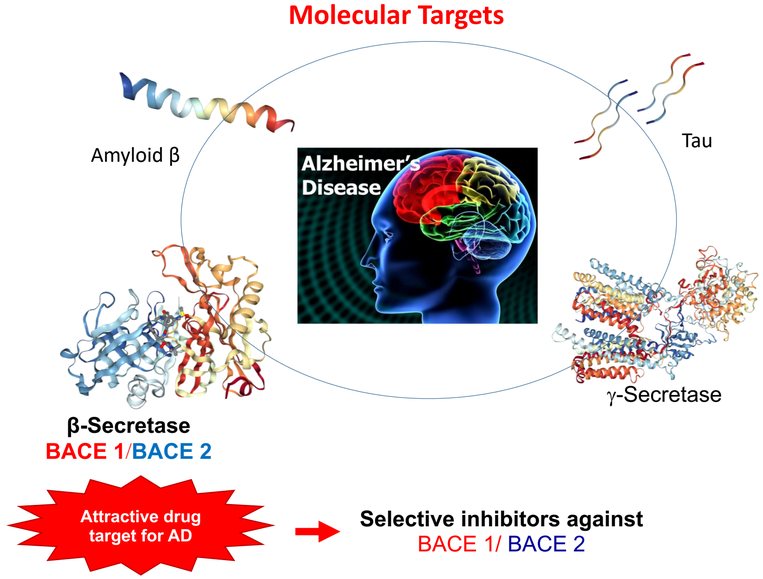
# Identification of selective inhibitors against BACE 1 over BACE 2 in Alzheimer's disease by Quantitative Structure-Activity Relationship (QSAR)

**Strategy for Diagnosis & Treatment in Alzheimer's diseases (AD)**




Modern **drug discovery** strategies

**Ligand Based (LB)**
(Information of Ligands Required)
- QSAR
- Pharmacophore modeling

Structure-Based (SB)
(3D Structure of Target Required)
- Docking
- Molecular Dynamics
- Pharmacophore modeling

To find/develop a hit or lead compound as drug candidate

Some steps of the drug discovery process require the use of **Machine Learning** techniques to construct statistically validated models

**Machine Learning**

**Supervised**
- ✓ Multiple Linear Regression Analysis

**Unsupervised**
- ✓ k-means clustering
- ✓ Hierarchical clustering

**We aim to develop Quantitative Structure-Activity Relationship (QSAR) models to Identification of selective inhibitors against BACE 1/ BACE 2 in Alzeheimer's disease for a data set of N-Phenylpicolinamide derivatives**

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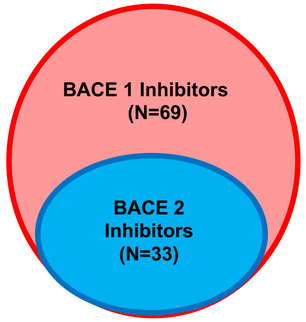
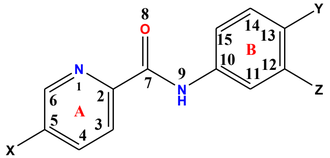
## Input Data Set




## Pharmacophore Derivatives

### N-Phenylpicolinamide



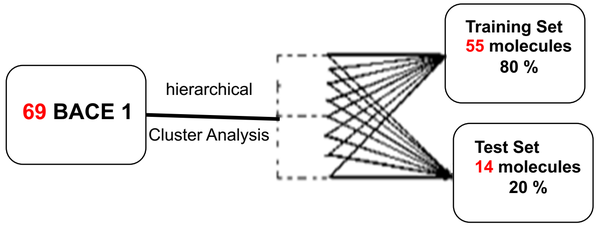

**A:** an **(hetero)aromatic ring**, **B**: an **(hetero)aromatic ring** and an **amide linker** is installed between A- and B-rings allowing the B-ring to enter deep into the pocket.
**X, Y, Z:** Substituent groups, **Pòsition 4**: C or N atom

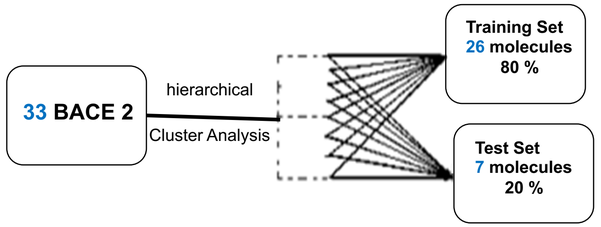
## Estimation of molecular properties (descriptors)

| BLOCK | TOTAL | SELECTION | EXCLUDE |
|---|---|---|---|
| 1. Constitutional indices | 50 | 14 | 36 |
| 2. Ring descriptors | 35 | 5 | 30 |
| 3. Geometrical descriptors | 38 | 0 | 38 |
| 4. Randic molecular profiles | 41 | 0 | 41 |
| 5. Functional group counts | 154 | 1 | 153 |
| 6. Pharmacophore descriptors | 165 | 3 | 162 |
| 7. 2D Atom Pairs | 1596 | 4 | 1592 |
| 8 3D Atom Pairs | 36 | 0 | 36 |
| 9. Charge descriptors | 15 | 0 | 15 |
| 10. Molecular properties | 27 | 11 | 16 |
| 11. Drug-like indices | 30 | 6 | 24 |
| 12. Chirality descriptors | 70 | 0 | 70 |
| TOTAL | 2257 | 44 | 2213 |

Exclusion criteria:
- At least one value **as zero**
- **Constant values**
- **Not applicable**


## Selection of training and test sets using Cluster Analysis




Cluster analysis is used in QSAR models to build the training and test sets as well as to determine the structural diversity of the dataset

- ✓ Compounds with biochemical activity below 1 μM were selected for further inhibition assay
- ✓ The $IC_{50}$ value is the concentration of compound which inhibits BACE 1 and BACE 2 binding by 50 %
- ✓ In our study, **the negative logarithm of the biological activity, $pIC_{50}$**, was used as the dependent variable to determine **QSAR correlation equations**
- ✓ Active molecule (pIC50 greater or similar than 6) and inactive molecule (pIC50 lower than 6)

Bioorganic & Medicinal Chemistry Letters. Volume 29, Issue 6, 15 March 2019, Pages 761-777

- ➢ The two-dimensional (2D) chemical structures of the inhibitors were generated using ChemDraw Ultra and saved in mol format.
- ➢ The 3D structure of each inhibitors were obtained by the geometrical optimization of each molecule using Kohn-Sham's DFT B3LYP/6-31G method included in Gaussian 09 program routines

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## Significant and Predictive QSAR model of BACE 1 inhibitors

$PIC_{50}$ = - 0.44 **F03[C-C]** + 0.60 **MR99**+ 0.19 **TPSA(Tot)** + 0.45 **LOGP** + 2.78 **LLS_02**-3.13

**Training sets :** n=55; R=0.90; $R^2$ = 0.81; s=0.26; F=42.71; Q2=0.76; P=0.00

**Test sets:** n=14; R=0.80; $R^2$ =0.64; s=0.70; F=21.43

| **F03[C-C]** | **MR** | **TPSA** | **LOGP** | **LLS_02:** A lead-like score (**8** rules) |
|---|---|---|---|---|
| Frequency of C - C at topological distance 3 | Molar Refractivity | Topological polar surface area using N,O,S,P polar contributions | Octanol/Water partition coefficient | $LS = \frac{nRules}{tRules}$ nRules: *number* of satisfied rules. tRules: total number of rules |
| **Electronic** (-) | **Steric** (+) | **Electronic** (+) | **Lypophilicity** (+) | **Lypophilicity-Steric-Electronic rules** (+) |

## Significant and Predictive QSAR model of BACE 2 inhibitors

$PIC_{50}$ = -2.05 **SCBO** +1.29 D/Dtr06 +8.94 **DLS_cons** +7.07 **LLS_01** -10.85 **QEDu** + 9.53

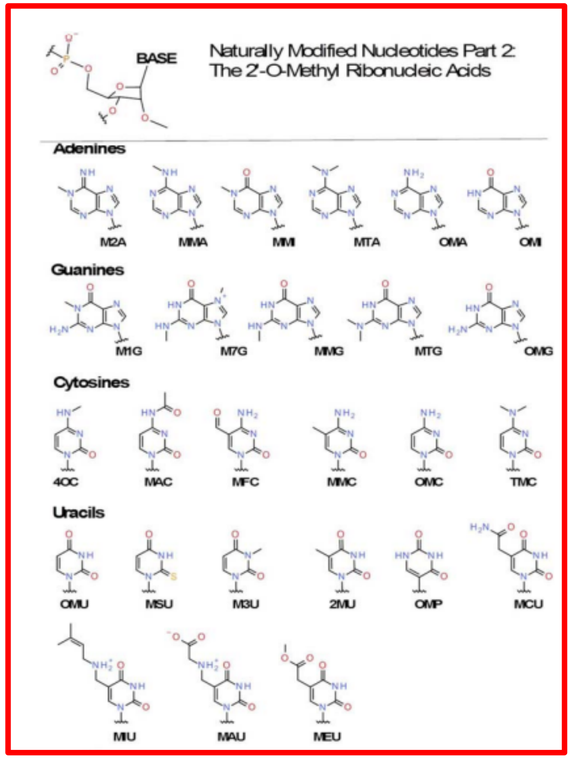
**Training sets**: n=28; R=0.91; $R^2$ = 0.83; s=0.42; F=22.47; Q2=0.75; P=0.00

**Test sets**: n=6; R=0.92; $R^2$ = 0.85; s=0.48; F=22.98

| **SCBO**: Sum of Conventional Bond Orders (H-depleted) | **D/Dtr06**: Distance/Detour ring index of order 6 | **DLS_cons**: DRAGON consensus **Drug-Like Score** (7 rules) | **LLS_01**: modified **Lead-Like Score** (6 rules) | **QEDu**: Quantitative Estimation of **Drug-likeness** (unweighted) (8 rules) |
|---|---|---|---|---|
| | | $LS = \frac{nRules}{tRules}$ nRules: *number* of satisfied rules tRules: total number of rules | | |
| **Steric** (-) | **Steric** (+) | **Lypophilicity-Steric-Electronic** (+) | **Lypophilicity-Steric-Electronic** (+) | **Lypophilicity-Steric-Electronic** (-) |

- Challenges for BACE1 inhibitors, notably achieving central penetration and avoiding toxicity, been progressively overcome in the past 10 years
- The most recent progress was made in getting high BACE1/BACE2 selectivity, which further reduces the toxicity risk.

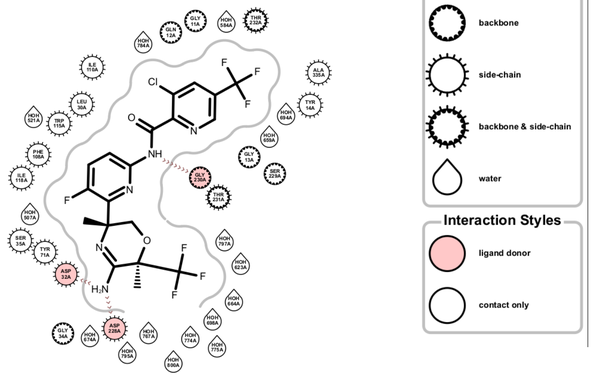
**157 Modified Ribonucleotides** → **Five Selective β-Secretase (BACE1) Inhibitors over BACE2**




Journal of Computational Chemistry 2016, DOI: 10.1002/jcc.24307

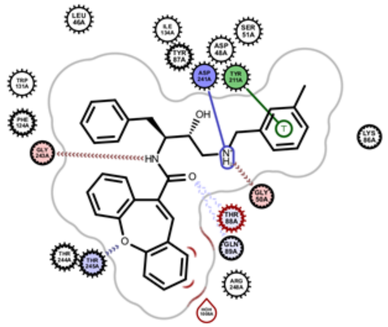
## Several BACE1/BACE 2 inhibitors have been progressed into clinical trials

### Clinical Trials BACE 1 INHIBITOR






### Clinical Trials BACE 2 INHIBITOR



**Toxicity**
**Lack of Efficacy**

Frederik Rombouts , Ken-ichi Kusakabe , Chien-Chi Hsiao & Harrie J. M. Gijsen (2020): Small-molecule BACE1 inhibitors: a patent literature review (2011 to 2020), Expert Opinion on Therapeutic Patents, DOI: 10.1080/13543776.2021.1832463

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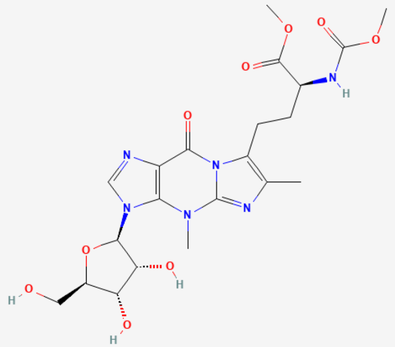
## Example of Selective β-Secretase (BACE1) Inhibitors over BACE2

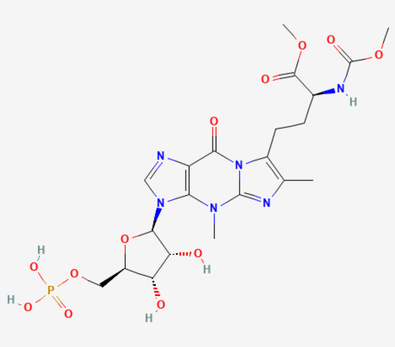
**BACE $1_{Cal.}$ = 10.00**
**F03[C-C]/10 = 2**
**MR99/10 = 13.06**
**TPSA(Tot)/10 = 24.80**
**MLOGP = - 0.60**
**LLS_02 = 0.63**

**BACE $1_{Cal.}$ = 8.50**
**F03[C-C]/10 = 2**
**MR99/10 = 11.97**
**TPSA(Tot)/10 = 19.17**
**MLOGP = - 0.89**
**LLS_02 = 0.75**

**YYG**



**YYG-P**

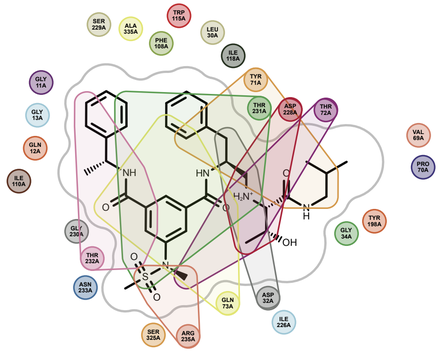


**BACE $2_{Cal.}$ = 4.65**
**SCBO/10 = 5.20**
**D/Dtr06/100 = 0.92**
**DLS_cons = 0.50**
**LLS_01= 0.17**
**QEDu = 0.10**

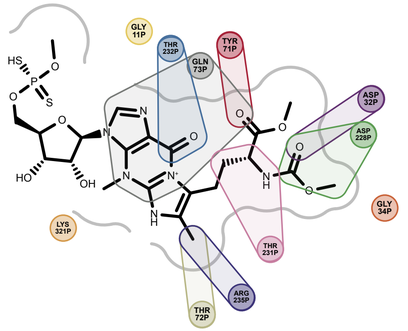
**BACE $2_{Cal.}$ = 5.75**
**SCBO/10 = 4.70**
**D/Dtr06/100 = 0.80**
**DLS_cons = 0.62**
**LLS_01= 0.17**
**QEDu = 0.18**

## Possible binding mode of YYG modified nucleotide at the β-Secretase (BACE1) active site: common contacted residues

BACE1-inhibitor (CHEMBL2179132)



BACE1-YYG (modified nucleotide)



## Conclusions

1) The combined possibilities of quantum and physicochemicals MD's, together with the Machine Learning techniques, allowed us to generate QSAR models, capable of discriminating between Selective β-Secretase (BACE 1) Inhibitors over BACE 2.

2) Hydrophobic, Steric and Electronic significant molecular descriptors included in the predictive QSAR model of BACE 1 and BACE 2 inhibitors allow the structural interpretation of the biological process, evidencing the main role of the shape of molecules, its hydrophobicity and its electronic properties in the transport and the Ligand–Receptor interaction.

3) QSAR models allowed the identification of five modified nucleotides as selective inhibitors against BACE 1/ BACE 2 in Alzheimer's disease. Phosphate group in the selective modified nucleotides have a positive impact in the inhibitor's activity. According the value of the significant molecular descriptors include in the QSAR models of BACE 1, a Phosphate group increases the MR, TPSA and LOG P values with a positive contribution to the BACE 1 inhibitor activity.

## Perspectives

1. Integrative model QSAR/structural data of BACE1(BACE2)-ligand complexes

2. MCSS calculations on BACE1 with modified nucleotides (in progress)