Novel lead optimization strategy of BACE I inhibitors for the treatment of Alzheimer's disease by Quantitative Structure-Activity Relationship (QSAR) and Physiologically-Based Pharmacokinetics (PBPK) modeling

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INTRODUCTION

Lead optimization is one of the most critical stages of drug discovery. The conventional lead optimization process normally starts with the identification of hit compounds which show decent K_i or IC_{50} for target proteins. Once identified, hundreds or thousands of derivatives are further synthesized to improve ADME(Absorption Distribution Metabolism Excretion)/PK(Pharmacokinetics) properties without compromising potency. However, this requires significant amounts of DMPK(Drug metabolism and Pharmacokinetics) resources and time due to the various *in vitro* ADME assays*in vivo* PK studies that must be evaluated. Therefore, several *in silico* approaches have been recently introduced to predict physicochemical properties and ADME properties in a high throughput manner for quick ranking-ordering of compounds by several pharmaceutical scientists using in-house models and global models supplied by commercial software.

In this study, we introduce an innovative *in silico*-based high throughput lead optimization strategy with QSAR and PBPK modelings using StarDrop™, ADMET predictor® and GastroPlus®.

EXPERIMENTAL METHOD

· For the proof-of-concept, a data set from the paper titled "Discovery of Cyclic Sulfone Hydroxyethylamines as Potent and Selective β-Site APP-Cleaving Enzyme 1 (BACE1) Inhibitors: Structure-Based Design and in Vivo Reduction of Amyloid β-Peptides, Journal of Medicinal Chemistry[1]" from the Journal of Medicinal Chemistry was used.

· First, a key scaffold of structure was defined based on literature[1]. After that, about 626 compounds structures were generated using an *in silico* library generation algorithm provide by StarDrop Nova™. A local predictive model of log(IC_{50}) was also made with published IC_{50} values using StarDrop Auto-Modeller™. The log(IC_{50}) values of 626 compounds generated by Nova™ were evaluated using this predictive model.

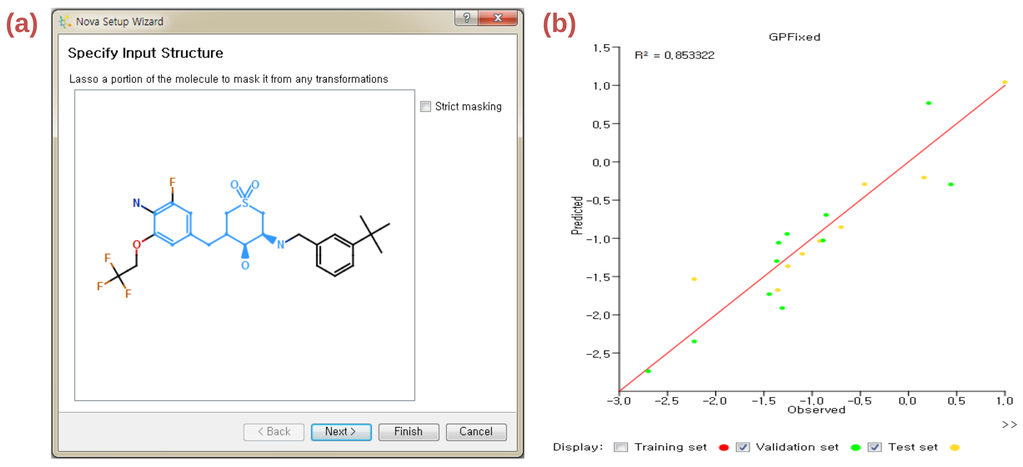


Figure 1. (a) In silico generation of new library compounds using StarDrop Nova™. (b) Development of an user-defined QSAR model for IC_{50} prediction using StarDrop Auto-Modeller™. The best predicted model was produced by the GPFixed algorithm. (R^2=0.85(validation set and test set).

· The compounds generated *in silico* were also rank-ordered based on the CNS Multi-Parameter Optimization (MPO)2 scores. A Final score was calculated for each compound by combining: (1) CNS MPO score, (2) the predicted IC_{50} (StarDrop™) and (3) intrinsic clearance predicted from ADMET predictor®.

$$\mathbf{MPO} = \sum \text{Score (clogP + clogD + PSA + MW + HBD + pKa)}$$

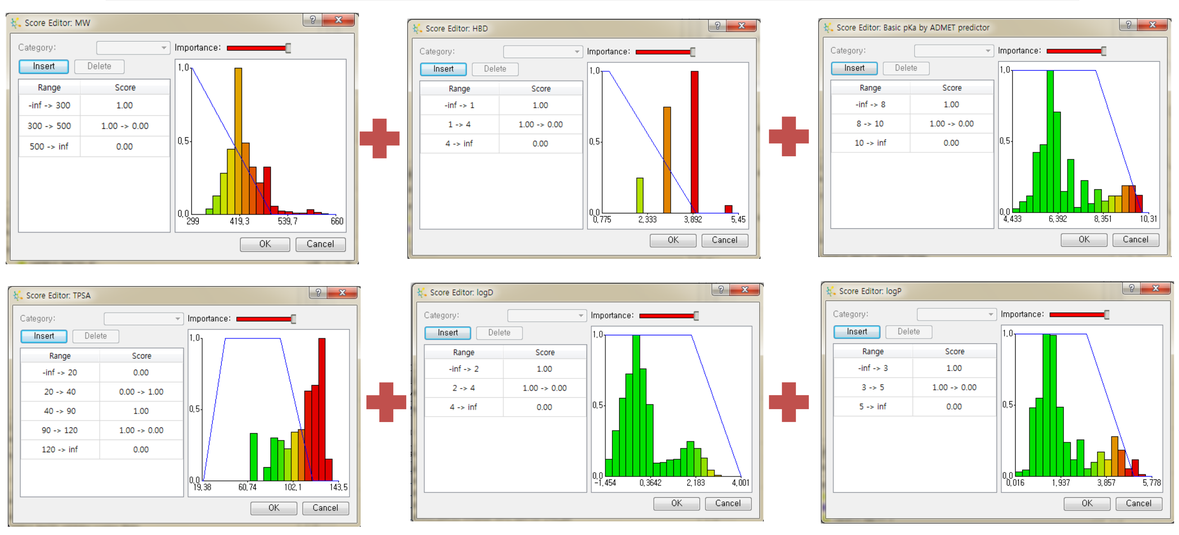
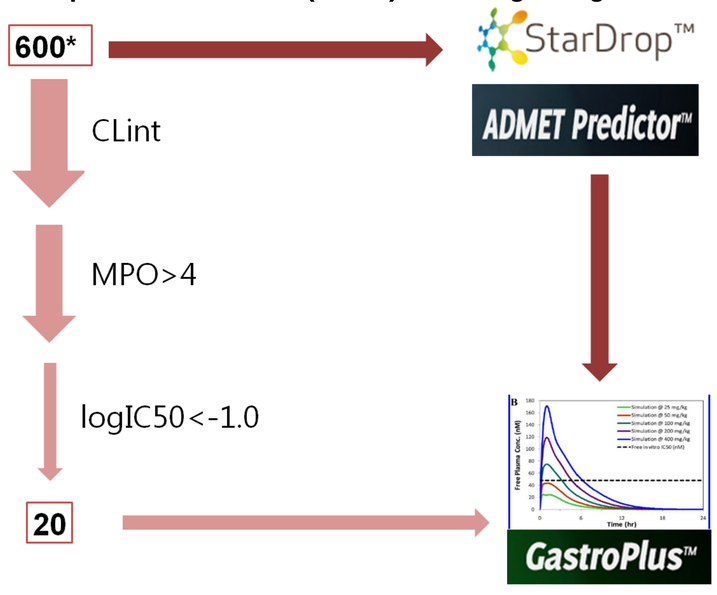


Figure 2. Production process of CNS Multi-Parameter Optimization(MPO) score.

· Top 20 compounds were selected based on the composite scores using MPO score, the predicted IC50 and the intrinsic clearance.

· To predicted the *in vivo* PK profiles of 20 compounds for various species, physiologically-based pharmacokinetics (PBPK) modeling using GastroPlus® was used.



*over 100,000 compounds can be synthesized using virtual library synthesis

Figure 3. Innovative CNS drug discovery strategy using in silico tools

REFERENCE

• Rueeger. H et al : **Discovery of cyclic sulfone hydroxyethylamines as potent and selective beta-site APP-cleaving enzyme 1 (BACE1) inhibitors: structure-based design and in vivo reduction of amyloid beta-peptides**. *J of Med Chem* 2012, **55**(7):3364-3386.

• Wager TT et al : **Moving beyond rules: the development of a central nervous system multiparameter optimization (CNS MPO) approach to enable alignment of druglike properties**. *ACS chemical neuroscience* 2010, **1**(6):435-449.

RESULT

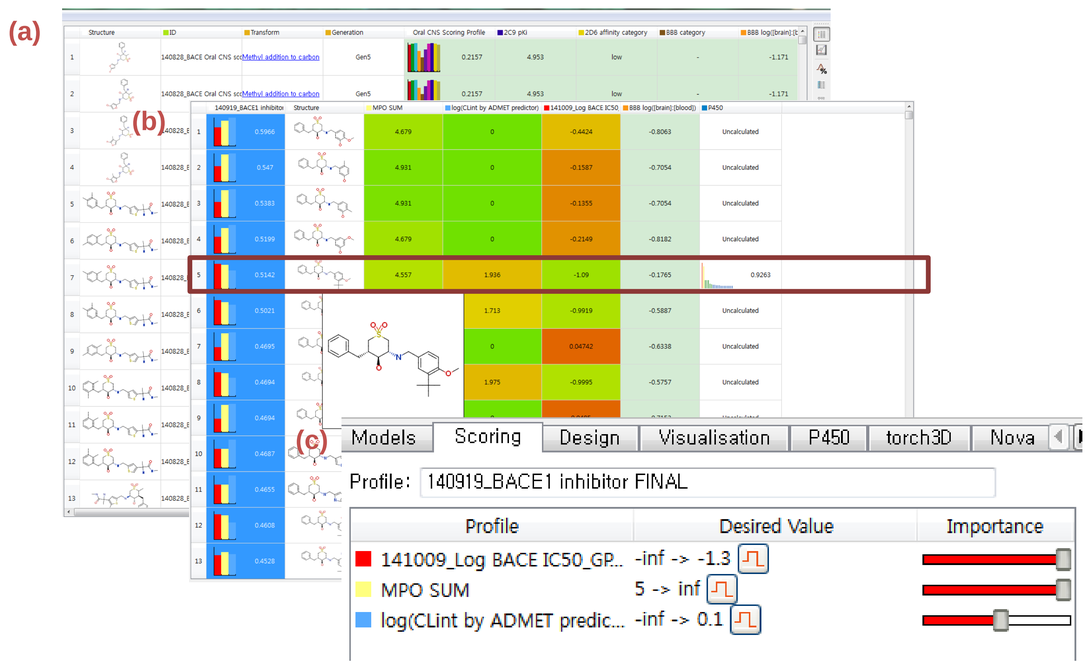


Figure 4. (a) 626 compounds virtually generated using StarDrop Nova™. (b) Compounds rank-ordered based on the composite scores. (c) The composite scoring rule used for BACE-1 inhibitors.

Finally, the top 5 of these 20 compounds were selected based on global ADME models as well as global BBB penetration models (such as log([Brain]:[Blood]) model) and were applied to *in vivo* PK profile prediction using GastroPlus® PBPK modeling. Metabolic stability is another key parameter to optimize during lead optimization process. Figure 5 demonstrates an example of *in silico* metabolic soft spot prediction for one of the top 5 compounds selected for PBPK modeling.

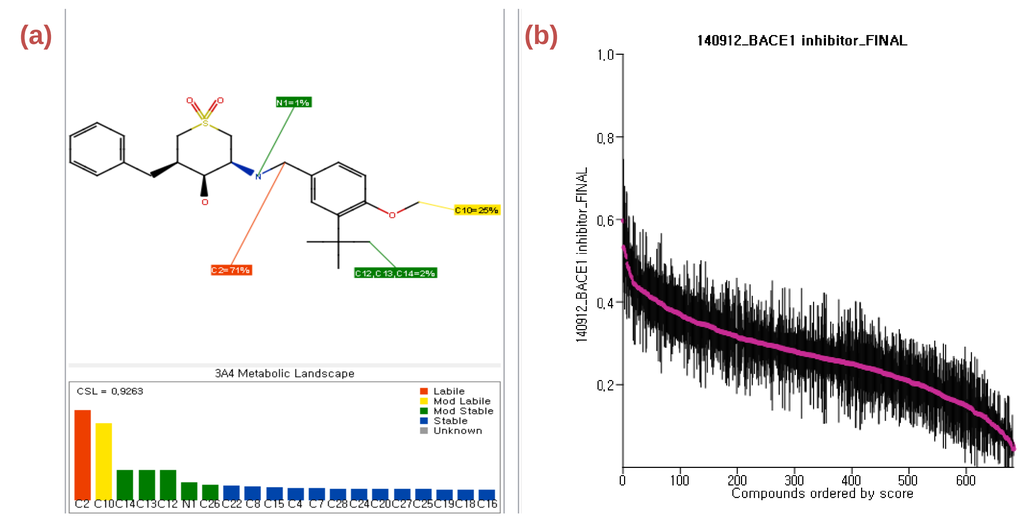


Figure 5. (a) Metabolic soft spot analysis of compound 5 using StarDrop P450™. (b) Score distribution of all compounds tested by user-defined scoring rule and global ADME/CNS models.

PK profiles were predicted using GastroPlus® in mouse, rat, dog and human. Simultaneously, the amount of dissolution and compartmental absorption can be predicted.

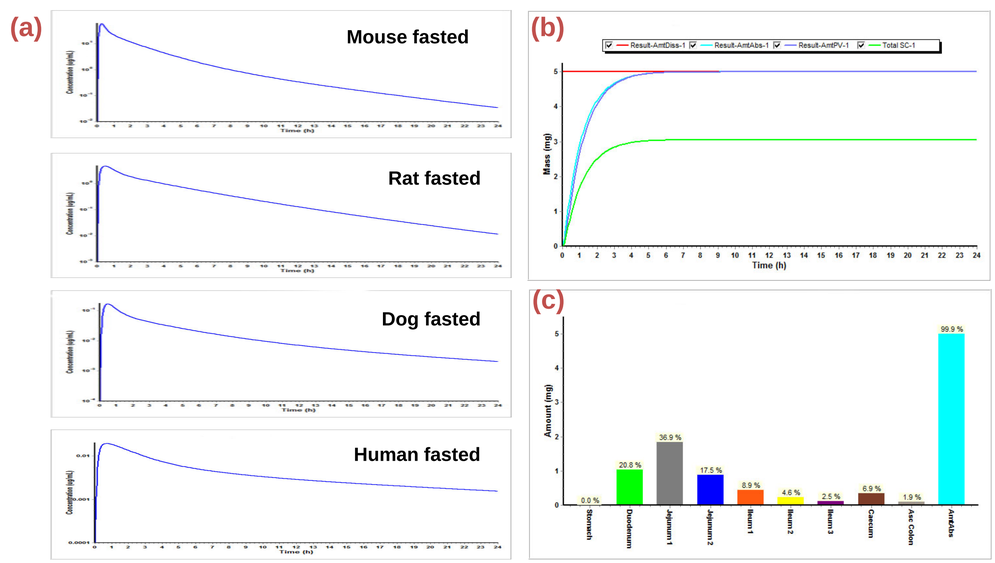
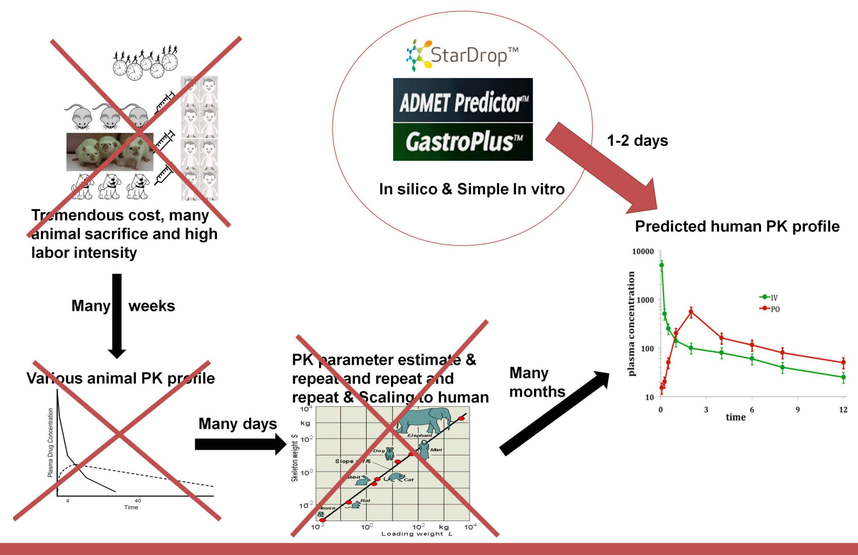


Figure 6. (a) PK profiles of compound 5 in four species (mouse, rat, dog and human) using GastroPlus ® PBPK modeling. (b) Absorption and dissolution profiles predicted in human PBPK model. (c) Relative compartmental absorption predicted in human.

CONCLUSION

Innovative *in silico* strategy for high throughput lead optimization was evaluated as a proof-of-concept using BACE-1 inhibitors. The proposed strategy would be very helpful to assist lead optimization efforts during early drug discovery.

Novel strategy of drug discovery in early stage



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