# CHEMICAL FUNCTION BASED PHARMACOPHORE MODELS OF V1a VASOPRESSIN ANTAGONISTS

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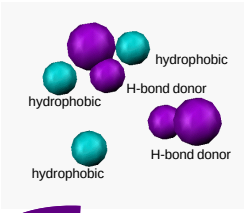
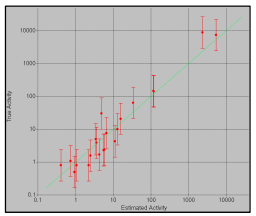
## INTRODUCTION

The neurohypophyseal hormone arginine vasopressin (AVP) is a cyclic nonapeptide that exhibits a high degree of functional diversity through interaction with specific receptors (currenty classified into V1a vascular, V1b pituitary, V2 renal and oxytocin receptors) that belong to the G protein-coupled receptor (GPCR) superfamily [1,2]. AVP exerts a variety of physiological effects and plays therefore an important role in congestive heart failure, hypertension, edema, and the syndrome of inappropiate antidiuretic hormone secretion. Hence, central interest is being focused on the development of non-peptide antagonists for these GPCRs [3].

### CATALYST Pharmacophore Model and Regression Analysis

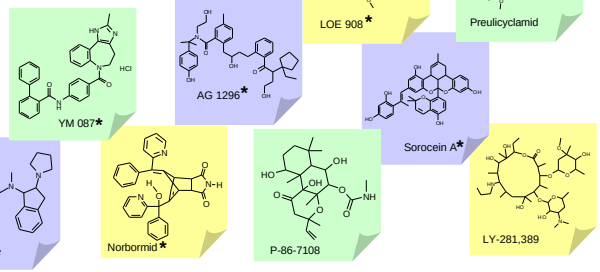


*Corr. factor:0.966*
*Total cost: 107.39*
*RMS: 0.680*
*Fix cost: 101.818*
*Null cost: 134.791*

3D Structure Database Search
**DERWENT WDI**
48405 Compounds

Examples of retrieved compounds (* known to be active ...)

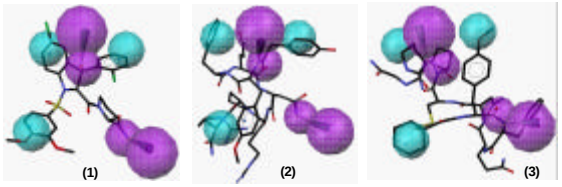



## METHODS

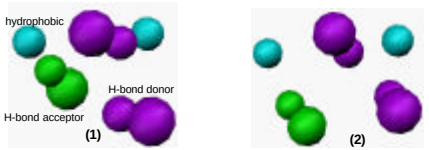
***Training Set:*** Pharmacophore models were generated using 17 structures of peptide and non-peptide ligands of the vasopressin V1a receptor exhibing a wide range of binding affinities from 0,8 nM to 8,8 µM [4].

***HypoGen* and *HipHop* algorithm** implemented in the Catalyst™ [5] software.

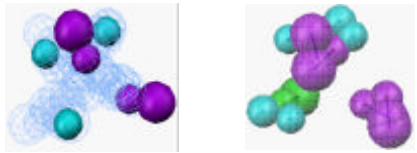
**Functions:** *H-Bond Acceptor*, *H-Bond Donor* and *Hydrophobic*




***Mappings of selected compounds of the training set :***
(1) SR 49059 - non-peptide antagonist, (2 ) 4- HO-LVA - linear peptide antagonist and (3) Manning - cyclic peptide antagonist



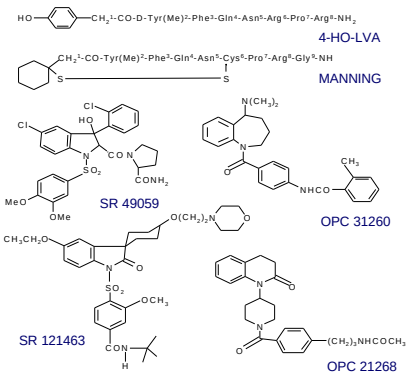

***Common Features Hypotheses from two different training sets***
(1) SR 49059 and 4-HO-LVA (2) SR49059 and Manning



***ShapeQuery***
derived from SR49059

***HipHop Hypothesis and HypoGen Hypothesis compared***

### Examples of Training Set Structures




| COMPOUNDS | Ki (nM) |
|---|---|
| 4-OH-LVA | 0.5 |
| tBaa-(D)Y(Et)FVNKPR | 0.8 |
| Phaa-(D)Y(Me)FQNRPRY | 0.8 |
| Phaa-(D)Y(Et)FQNKPR | 0.8 |
| SR 49059 | 1.1 |
| MANNING | 1.6 |
| AVP | 1.7 |
| LVP | 2.3 |
| Phaa-(D)Y(Et)FVNKPY | 2.4 |
| d(CH$_2$)$_5$[Y(Me)TOY]AVT | 3.9 |
| d[D-3Pal]VP | 4.3 |
| AVT | 5 |
| d(CH$_2$)$_5$[Y(Me)TO]AVT | 7.6 |
| dVDAVP | 10 |
| dDAVP | 21 |
| d(CH$_2$)$_5$[(O)FFRrA]AVP | 30 |
| OXYTOCIN | 64 |
| OPC 31260 | 142 |
| VPA-985 | 147 |
| SR 121463A | 7375 |
| OPC 21268 | 8800 |

## RESULTS

The resulting pharmacophore models were used as 3D database search queries: The Derwent World Drug Index (WDI) was searched to identify potent vasopressin V1a receptor antagonists. Expectedly, several highly potent biologically active antagonists, that had not been used for the pharmacophore model generation were retrieved and the predictive power of our models was confirmed. Thus it can be expected that the other hits will also exhibit V1a activity. Moreover, this concept may also be extended to search virtual 3D databases. This approach may represent a suitable method for the design of novel V1a antagonist lead structures.

### REFERENCES

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4 Thibonnier, M. et al., in *Vasopressin and Oxytocin*, Zingg, H. et al., Eds., Plenum Press, 1998, **449**: 251-276
5 Molecular Simulations Inc., San Diego, CA, USA (1997)

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