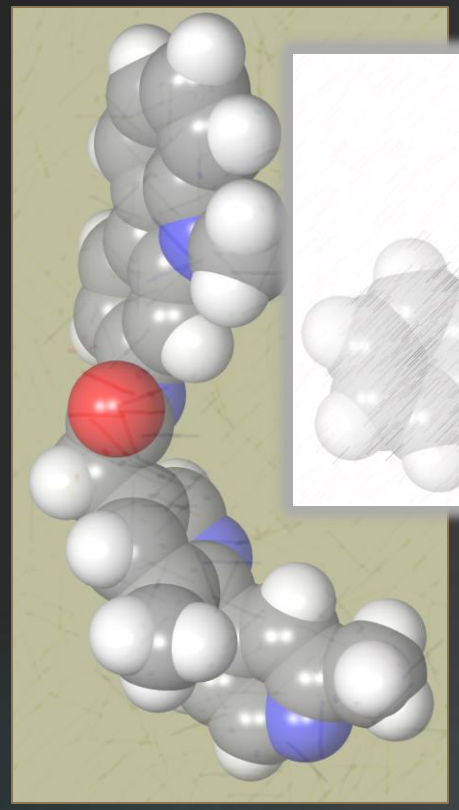

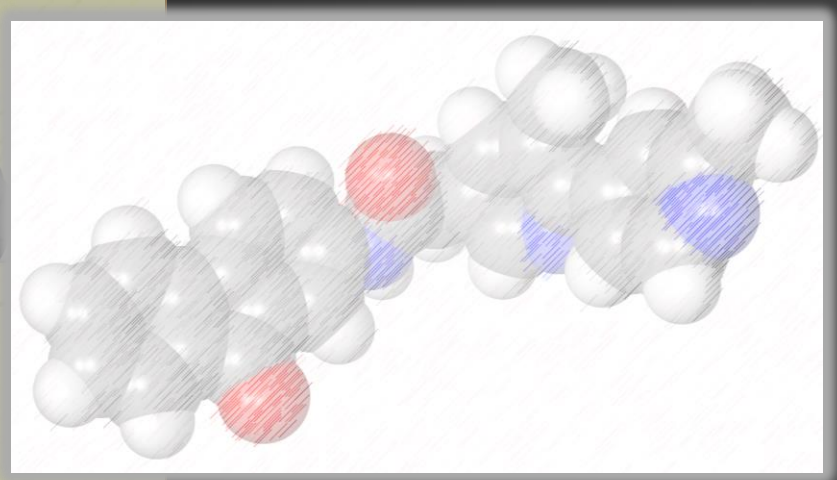

In silico ligand-based methods targeting porcupine receptor inhibitors with potential anticancer effect

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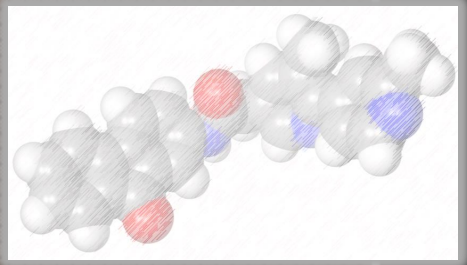
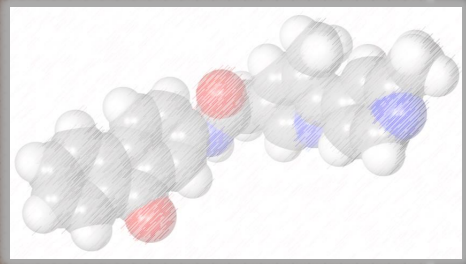
ABSTRACT



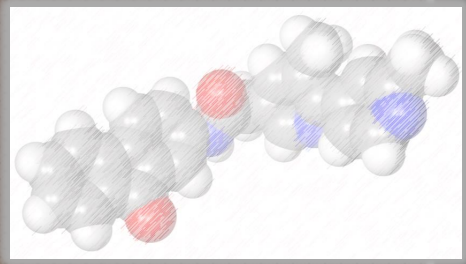
Porcupine is a protein belonging to the O-acyltransferase family, involved in catalyzing of palmitoylation of WNT proteins. WNT signaling has significant roles in many physiological functions, e.g.: hematopoiesis, homeostasis, neurogenesis, and apoptosis. Anomalous WNT signaling has been observed to be related to tumors generation, metabolic and neurodegenerative disorders. Therefore, compounds that inhibit this pathway are of great interest for the development of therapeutic approaches. For a better understanding of the common traits of such compounds, we have undertaken an *in silico* study in order to develop a valid ligand-based pharmacophore model based on a series of porcupine inhibitors. The best pharmacophore hypothesis found after the 3D QSAR validation process is represented by the following features: one hydrogen bond donor (D), three rings (R) and one hydrophobic centroid (H). The 3D-QSAR model obtained using the DRRRH hypothesis shows statistically significant parameters: correlation coefficients for the training set: R^2 of 0.90, and a predictive correlation coefficient for the test set, Q^2 of 0.86. The assessment of the pharmacophore model was also done and provided very reliable metrics values (Receiver Operating Characteristic – ROC of 1; Robust Initial Enhancement – RIE of 17.97). Thereby, we obtained valuable results which can be further used in the virtual screening process for the discovery of new active compounds with potential anticancer activity.

OBJECTIVES



1. To develop a good pharmacophore hypothesis for porcupine inhibitors
2. To validate the hypothesis by 3D QSAR model generation and by Enrichment calculations.
3. To detect important features beneficial or detrimental for ligand-receptor interactions.

METHODS



LIGANDS PREPARATION

A dataset of 17 compounds [1] was the subject of computational analysis for pharmacophore generation.

The 2D structures of the compounds were drawn with Marvin Sketch (17.14, 2017), from Chemaxon [2].

The ligands preparation was realised using Ligprep software [3] of Schrödinger, by following the steps:

-optimization of the structures with OPLS_2005 force field,

-ionization with Epik at pH = 7.2± 0.2;

-generation of tautomers and stereoisomers.

PHARMACOPHORE GENERATION AND VALIDATION

Phase [4] with the option: "Develop Common Pharmacophore Hypotheses" was used for generation and validation of the pharmacophore hypotheses by the involvement of the atom-based QSAR module.

ConfGen [5] was engaged in generation of multiple conformers for each compound using default settings.

The compounds were considered active if the pIC_{50} value is > 8 and inactive if pIC_{50} value is <7.

An atom-based 3D-QSAR [6] analysis was carried out by using 1 partial least-squares (PLS) factor and a test set of approx. 28% of compounds chosen to cover the same range of activity as the compounds from the training set.

The Enrichment Calculator Panel [7] was used to assess the enrichment of active compounds in a screening process that includes a set of actives and a set of decoys (of 1000 compounds).

METHODS

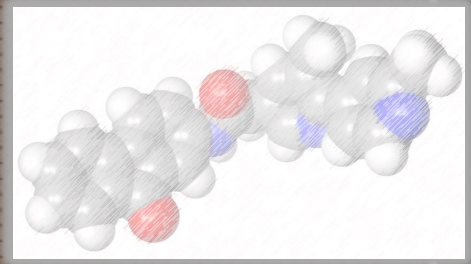
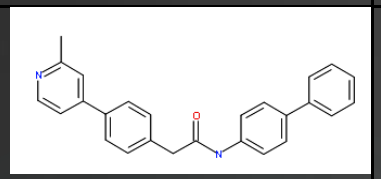
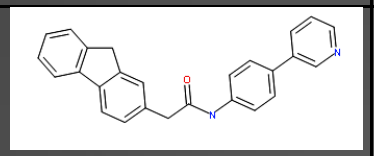
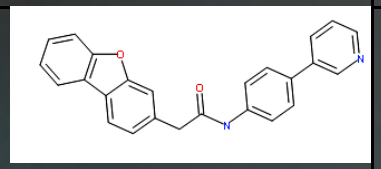
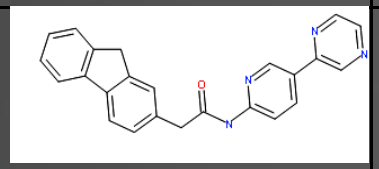
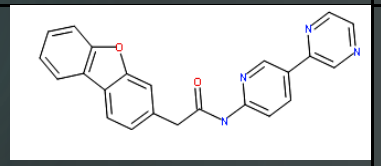
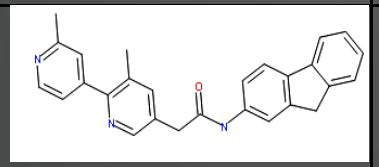
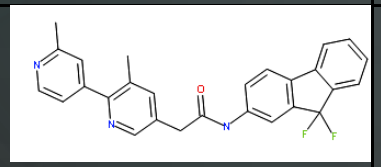
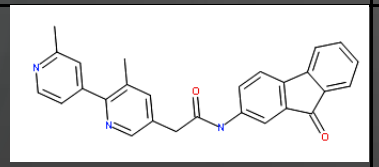
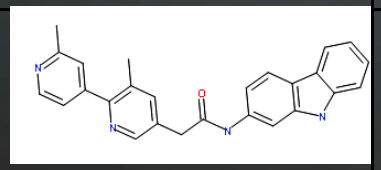
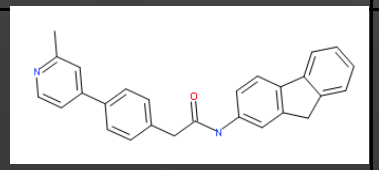
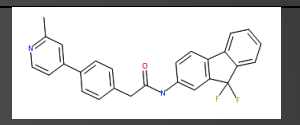
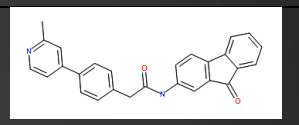
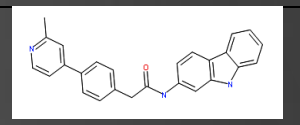
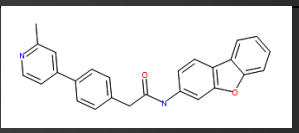
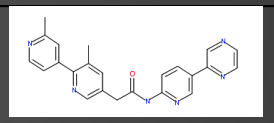
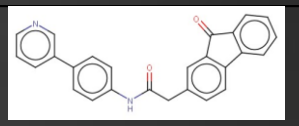
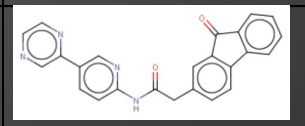
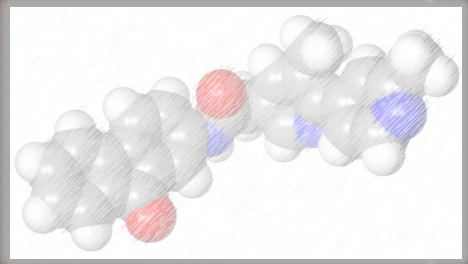


Table. 1 The 2D structure of the porcupine inhibitors from the dataset [1]

No	Structure	pIC_{50}	No	Structure	pIC_{50}
1		8.54	2		6.64
3		6.26	4		6.34
5		6.87	6		8.60
7		8.57	8		8.55
9		8.59	10		8.85

No	Structure	pIC_{50}	No	Structure	pIC_{50}
11		8.46	12		9.35
13		8.64	14		8.05
15		9.05	16		6.00
17		6.00			



RESULTS and DISCUSSIONS

Slide5

- The 2D structures of the porcupine inhibitors used to develop the pharmacophore model are shown in Table 1.

Slide7

- The best pharmacophore obtained is represented by DRRRH hypothesis presented in Figure 1 and its good statistical parameters are rendered in Table 2.

Slide8

- The correlation plot of experimental versus predicted activity is shown in Figure 2.

Slide9

- The important features for the ligand-receptor interactions are display in Figure 3.

RESULTS and DISCUSSIONS

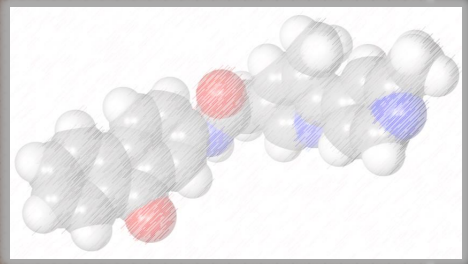


Table 2. The statistical parameters for DRRRH hypothesis

Hypothesis	SD	R^2	R^2cv	R^2scramble	Stability	F	RMSE	Q^2	Pearson-R
DRRRH	0.37	0.90	0.76	0.44	0.94	88.6	0.47	0.86	0.99

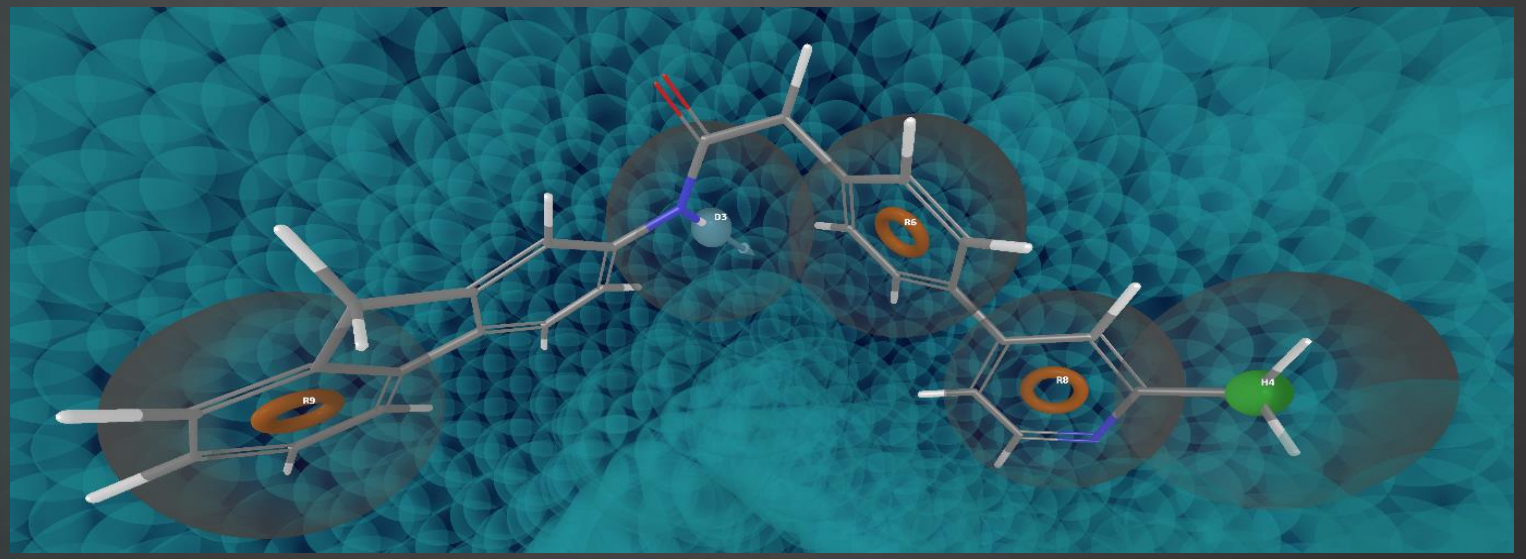
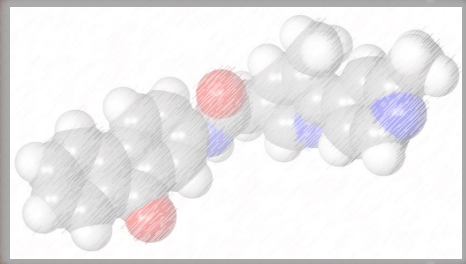


Figure 1. Compound 10, the best fitted on DRRRH hypothesis

RESULTS and DISCUSSIONS



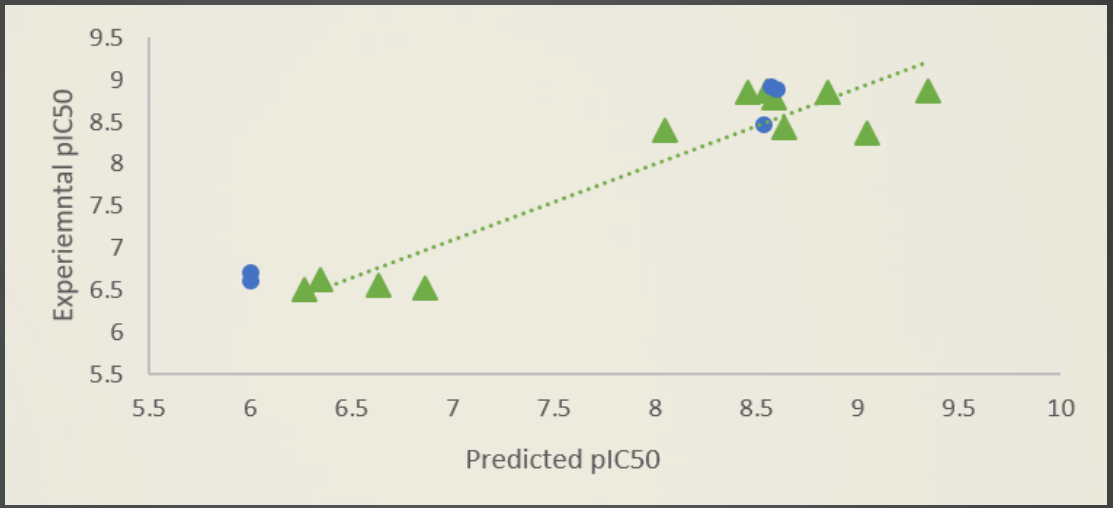
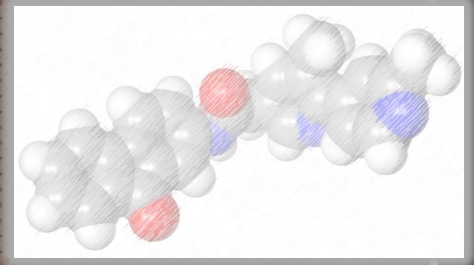


Figure 2. Correlation plot of experimental versus PHASE predicted activity of training set (green triangles) and test set (blue circles).

RESULTS and DISCUSSIONS



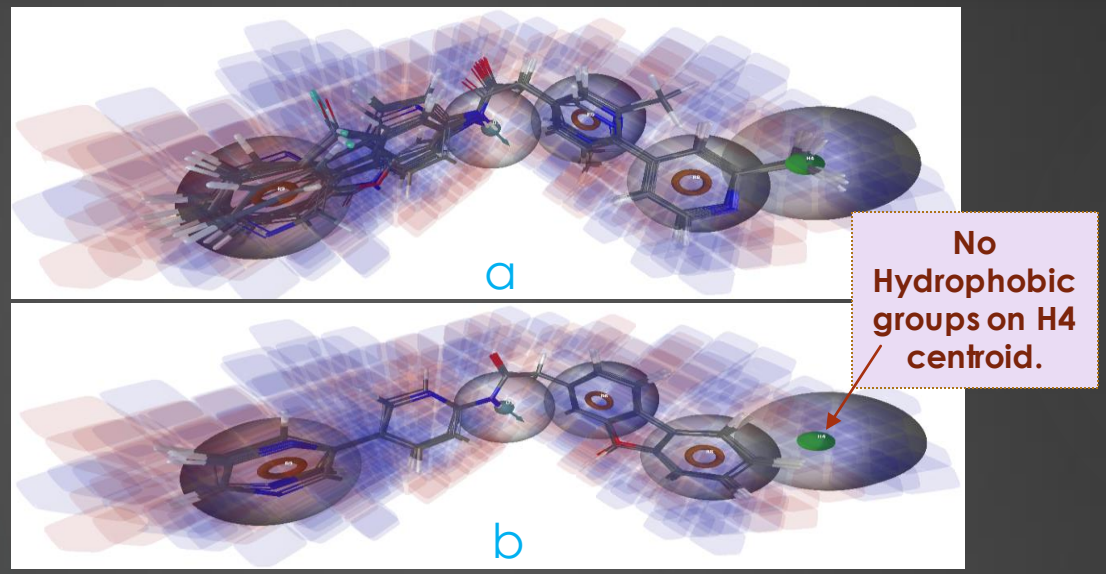
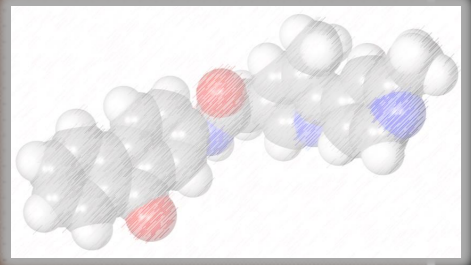


Figure 3. Compounds in the context of 3D-QSAR model: hydrogen bond donor property; hydrophobic property; electron withdrawing property. a. The active compounds aligned over DRRRH hypothesis; b. The inactive compounds aligned over DRRRH hypothesis. Blue cubes indicate positive coefficient (increase in activity), red cubes indicate negative coefficient (decrease in activity).

RESULTS and DISCUSSIONS



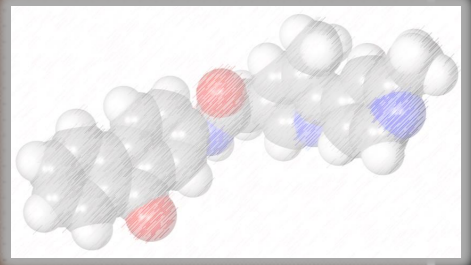
Evaluation of DRRRH pharmacophore hypothesis using Enrichment calculator

Table 3. Enrichment performance for the DRRRH pharmacophore hypothesis

BEDROC		
alpha=160.9	alpha=20.0	alpha=8.0
1.000	1.000	1.000
alpha*Ra		
1.751	0.218	0.087
Receiver Operator Characteristic (ROC)		
1.000		
Area under accumulation curve (AUAC)		
0.990		
Robust Initial Enhancement (RIE)		
17.970		
Count and percentage of actives in top N% of decoy results		
% Decoys		
1%	2%	5%
% Actives		
100	100	100

Count and percentage of actives in top N% of results		
% Results		
1%	2%	5%
% Actives		
90.9	100	100
Enrichment Factors with respect to N% sample size.		
% Sample		
1%	2%	5%
Enrichment factor (EF)		
92%	51%	20%
Enrichment factor for recovering x% of the known actives (EF*)		
1e+02	50	20
Modified enrichment factor (EF')		
1.8e+02	95	39
Efficiency in distinguishing actives from decoys (Eff)		
0.980	0.961	0.905

Conclusions



- *The best pharmacophore hypothesis has the following features: one hydrogen bond donor (D), three aromatic rings (R) and one hydrophobic (H) region (Figure 1).*

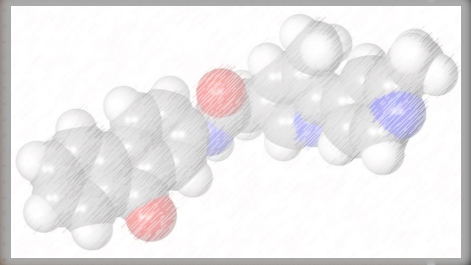
- *The 3D-QSAR model built using DRRRH hypothesis shows good statistically parameters: a correlation coefficient, R^2 of 0.90 for the training set and a predictive correlation coefficient, Q^2 of 0.86.*

- *Using the Enrichment Calculator Panel a very good evaluation and validation of the pharmacophore model was obtained.*

- *From the Figure 3b we can see that the inactive compounds are missing one pharmacophore feature (the hydrophobic H4 centroid), which lead to the conclusion that this characteristic is very important for the biological activity.*

- *Good statistical parameters were obtained (Table2), suggesting that the model is reliable in predicting novel inhibitors with potential anticancer activity, against Wnt signaling pathway.*

References



1. Z. Xu, J. Li, Y. Wu, Z. Sun, L. Luo, Z. Hu, S. He, J. Zheng, H. Zhang, X. Zhang, Eur. J. Med. Chem. 108 (2016) 154-165.

2. http://www.chemaxon.com

3. Schrödinger Release 2018-1: LigPrep, Schrödinger, LLC, New York, NY, 2018.

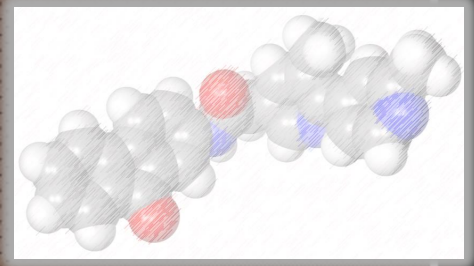
4. Schrödinger Release 2018-1: Phase, Schrödinger, LLC, New York, NY, 2018.

5. Schrödinger Release 2018-8: ConfGen, Schrödinger, LLC, New York, NY, 2018.

6. S.L. Dixon, A.M. Smondyrev, E.H. Knoll, S. N. Rao, D. E. Shaw, R.A. Friesner, J. Comput. Aided Mol. Des. 20 (2006) 647-671.

7. T. A. Halgren, R. B. Murphy, R. A. Friesner, H. S. Beard, L. L. Frye, W. T. Pollard, J.L. Banks, J. Med. Chem. 47 (2004) 1750–1759.

Acknowledgements



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