3D-QSAR STUDIES ON AMIDE AND UREA DERIVATIVES AS NAMPT INHIBITORS

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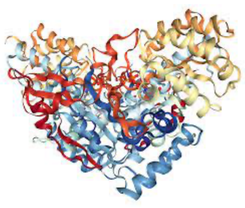
NAMPT



Nicotinamide phosphoribosyltransferase (NAMPT) is an important regulator enzyme in the mammalian NAD^+ synthesis pathway. Considering NAD^+ is involved in many cellular processes like cytokine production, metabolism, and aging, NAMPT has become a therapeutically important target for various diseases, particularly cancer [1]. Hence, numerous NAMPT inhibitors have been reported in the literature. However, the problems such as dose-dependent toxicity and side effect profile of these molecules, have sparked interest in discovering new inhibitors [2].

In this study, a statistically validated field-based 3D-QSAR model was generated using chemically diverse urea and amide derivatives as NAMPT inhibitors. The required features for NAMPT inhibition were evaluated using the model in terms of different interaction field contributions.

Field-Based 3D-QSAR Model

3D-QSAR Model Generation

A total number of 53 chemically diverse urea and amide derivatives as **NAMPT inhibitors,** IC_{50} values of which against have been determined human NAMPT enzyme, were collected from previous studies.

Dataset collection (53 NAMPT inhibitors)

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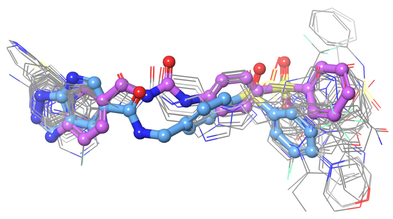
Dataset clustering

The IC_{50} values were converted into negative logarithm of IC_{50} (pIC_{50}). **pIC_{50} (from 4.95 to 9.00)**

The dataset was classified into five clusters to group chemically different NAMPT inhibitors.

The dataset was divided into **training (40)** and **test sets (13)** by ensuring that the sets get chemically and activity-wise similar compounds.



Assignment of traininig and test sets

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Docking based alignmnet

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3D-QSAR model generation

The 3D-QSAR model was created with the aligned dataset using partial least square (PLS) regression analysis. (Maximum PLS factor:6)

Extended Gaussian-based potential, consisting of steric, electrostatic, hydrophobic, H-bond acceptor, H-bond donor, and aromatic ring fields, was used as the molecular field type.

Statistical Analysis

Factors	SD	$r^2_{training}$	$r^2cv_{training}$	$r^2scramble$	Stability	F	P	$RMSE_{test}$	q^2_{test}	Pearson-r
1	0.684	0.615	0.431	0.191	0.946	60.8	2.1e-09	0.62	0.323	0.693
2	0.604	0.708	0.558	0.414	0.892	44.9	1.29e-10	0.52	0.516	0.781
3	0.519	0.790	0.556	0.593	0.866	45.2	2.75e-12	0.31	0.828	0.916
4	0.458	0.841	0.568	0.686	0.840	46.3	1.63e-13	0.30	0.846	0.927
5	0.403	0.880	0.519	0.770	0.780	50.2	9.83e-15	0.37	0.765	0.893
6	0.316	0.928	0.376	0.837	0.572	71.8	1.63e-17	0.53	0.506	0.812

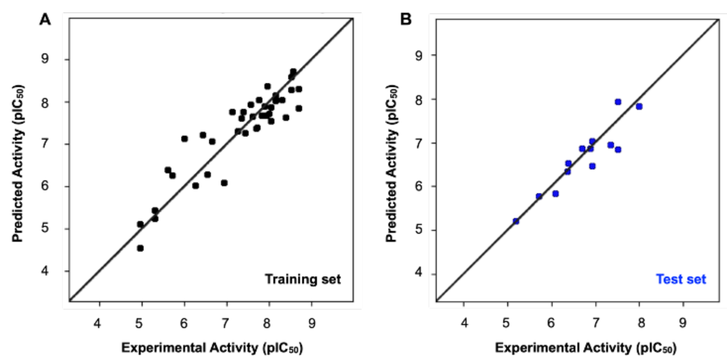
Validated model

($r^2 > 0.6$ and $r^2cv > 0.5$)[3]

No overfitting issue

(Stability ≥ r^2)

Good predictive model



Contour Map Analysis

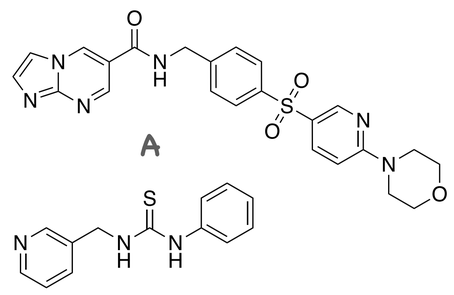
The molecular field contribution values indicate that the steric, electrostatic, hydrophobic, and HBA features of the molecules play a significant role in affecting biological activity.

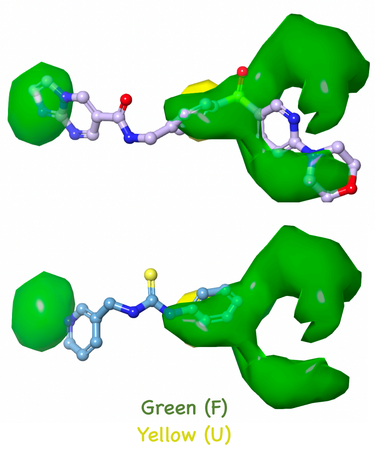
The contribution of potential field values for selected model

PLS factor	Steric	Electrostatic	Hydrophobic	HBA*	HBD*	Aromatic Ring
4	0.4655	0.1128	0.1105	0.1897	0.0170	0.1042

*HBA: Hydrogen bond donor, HBD: Hydrogen bond acceptor

The most (A) and **the least (B)** active NAMPT inhibitors in the dataset were overlaid on the contour maps to visualize **favored (F)/unfavored (U)** chemical features affecting biological activity.





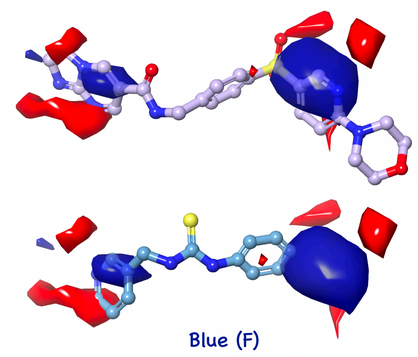
Green (F)
Yellow (U)

Steric

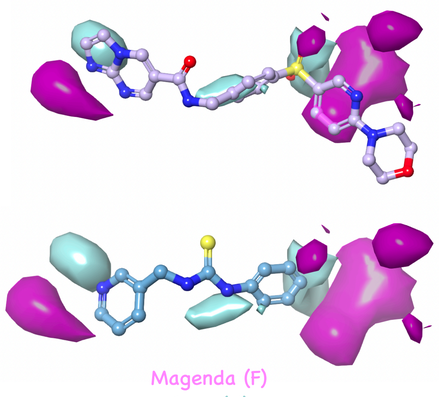
Molecule A occupies the favorable steric regions more than Molecule B, which indicates that steric occupation on the left and right green regions might be important for activity.

Electrostatic

Molecule B doesn't bear any electropositive group on the right blue region. In this region, electropositive groups might increase NAMPT inhibition activity.



Blue (F)
Red (U)



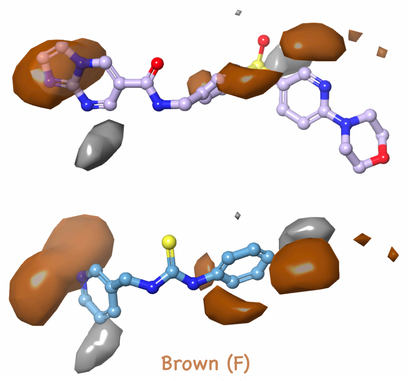
Magenda (F)
Cyan (U)

Hydrogen Bond Acceptor

Sulfonyl moiety, which is a hydrogen bond acceptor of Molecule B, occupies the favorable pink region. On the right pink region, extra group with hydrogen bond acceptor might increase activity.

Aromatic Ring

Aromatic rings of Molecule A occupy the favorable aromatic regions more than those of Molecule B. Apropriate orientation of aromatic rings in NAMPT inhibitors might be important for activity.



Brown (F)
Grey (U)

References

[1] Yaku, K., et al., NAD Metabolism in Cancer Therapeutics. Frontiers in Oncology, 2018; 8

[2] Gasparrini, M. and V. Audrito, NAMPT: A critical driver and therapeutic target for cancer. Int J Biochem Cell Biol, 2022;145:106189

[3] Golbraikh, A. and A. Tropsha, Predictive QSAR modeling based on diversity sampling of experimental datasets for the training and test set selection. J Comput Aided Mol Des, 2002;16(5-6):357-69.