XXXI Symposium
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Computer-Aided Drug Discovery

Development of a Probability Factor Based on Blind and Target-Site Docking Analysis for Improved IC50 Prediction of Candidate Competitive Enzyme Inhibitors

D. Amanatidou[1], P. Eleftheriou[1], P. Kefalou[1], A. Geronikaki[2], A. Petrou[2], D.Lazari[3], T. Papagrigoriou[3], K. M. Dimitriadis[3]

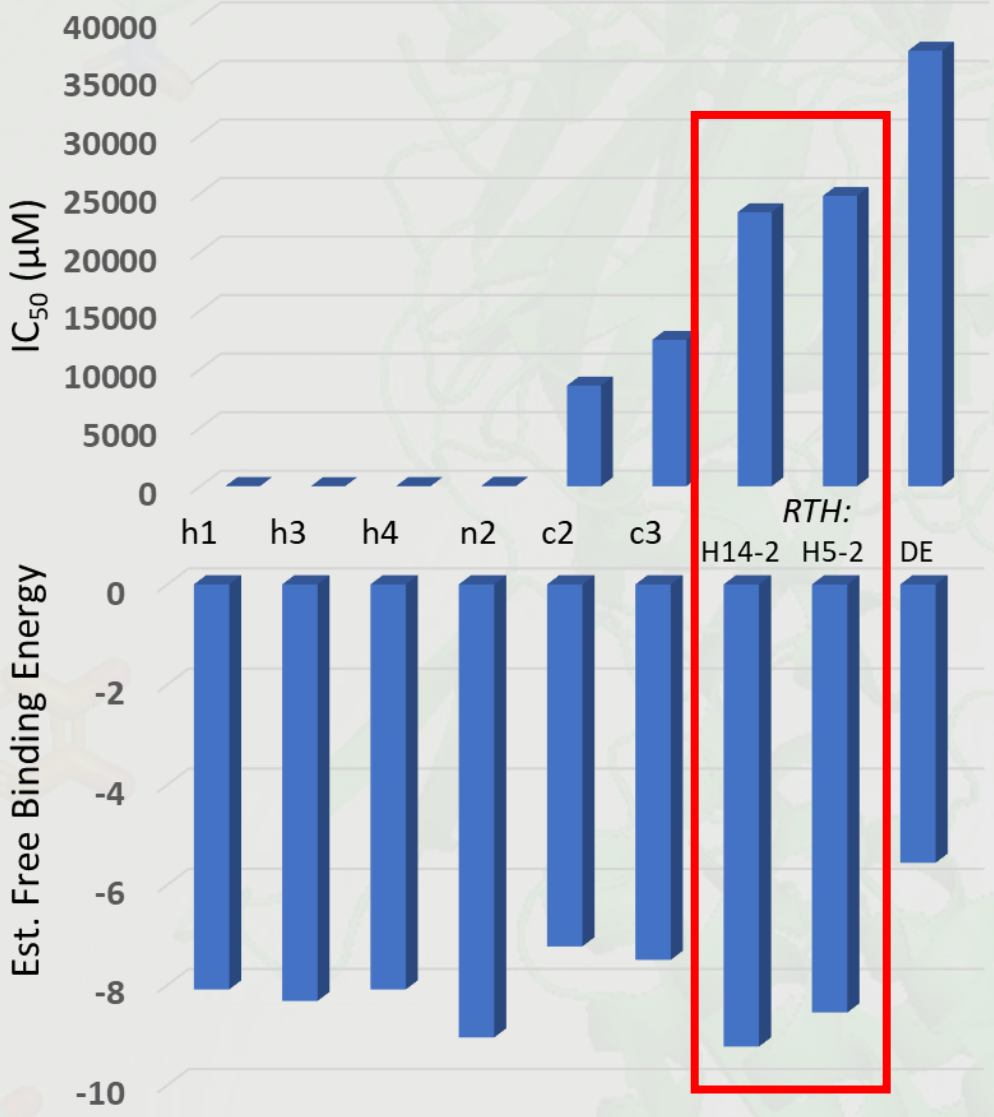
1. Department of Biomedical Sciences, School of Health, International Hellenic University, 52400 Thessaloniki, Greece.
2. Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece.
3. Department of Pharmacognosy-Pharmacology, School of Pharmacy, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece.

Introduction:

Molecular docking is a widely used method for screening compounds in order to identify promising enzyme inhibitors for novel drug development. Docking to a specific binding target, such as an **active** or **allosteric site**, is often applied for compound screening.

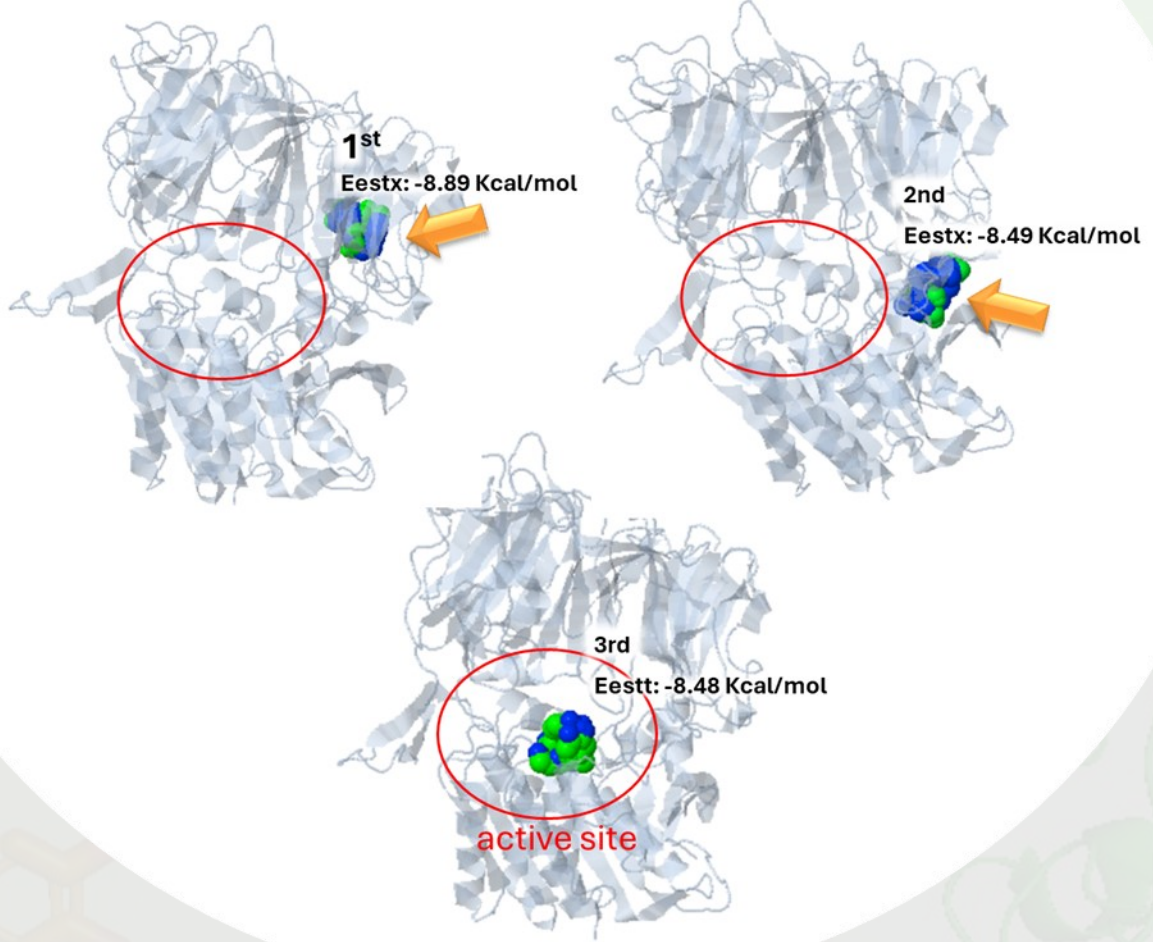
Problem:

However, this approach has the drawback that compounds showing promising in silico results may not be truly effective *in vitro*.



Problem:

By simple targeted-Docking Analysis,
compounds showing promising in silico results may not be truly effective *in vitro.*



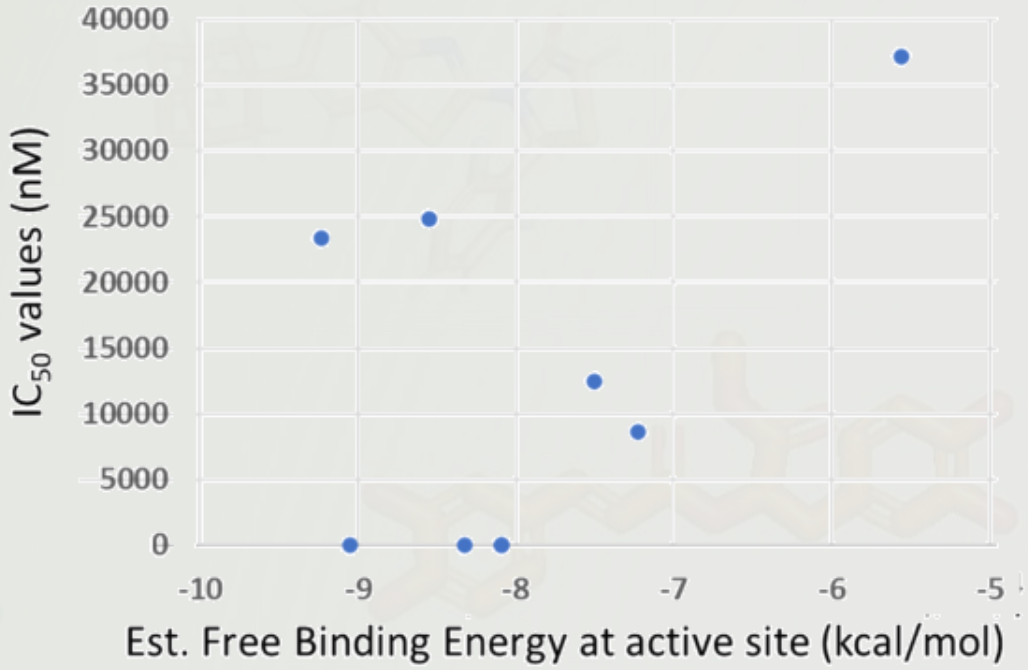
This **may result from preferential binding to alternative** enzyme **sites** that do not cause inhibition.

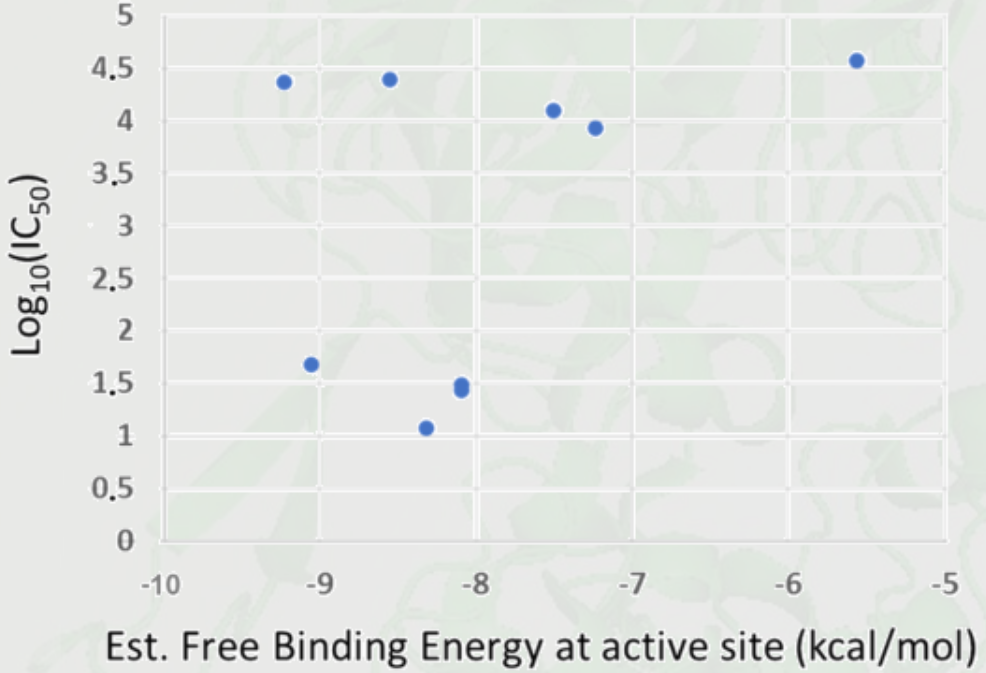
Blind docking across the entire enzyme can reveal these preferred sites.

Purpose:

To develop a more accurate predictive model by incorporating the binding energy of each tested compound at the target binding site as well as at alternative, more preferable binding sites.

Results:



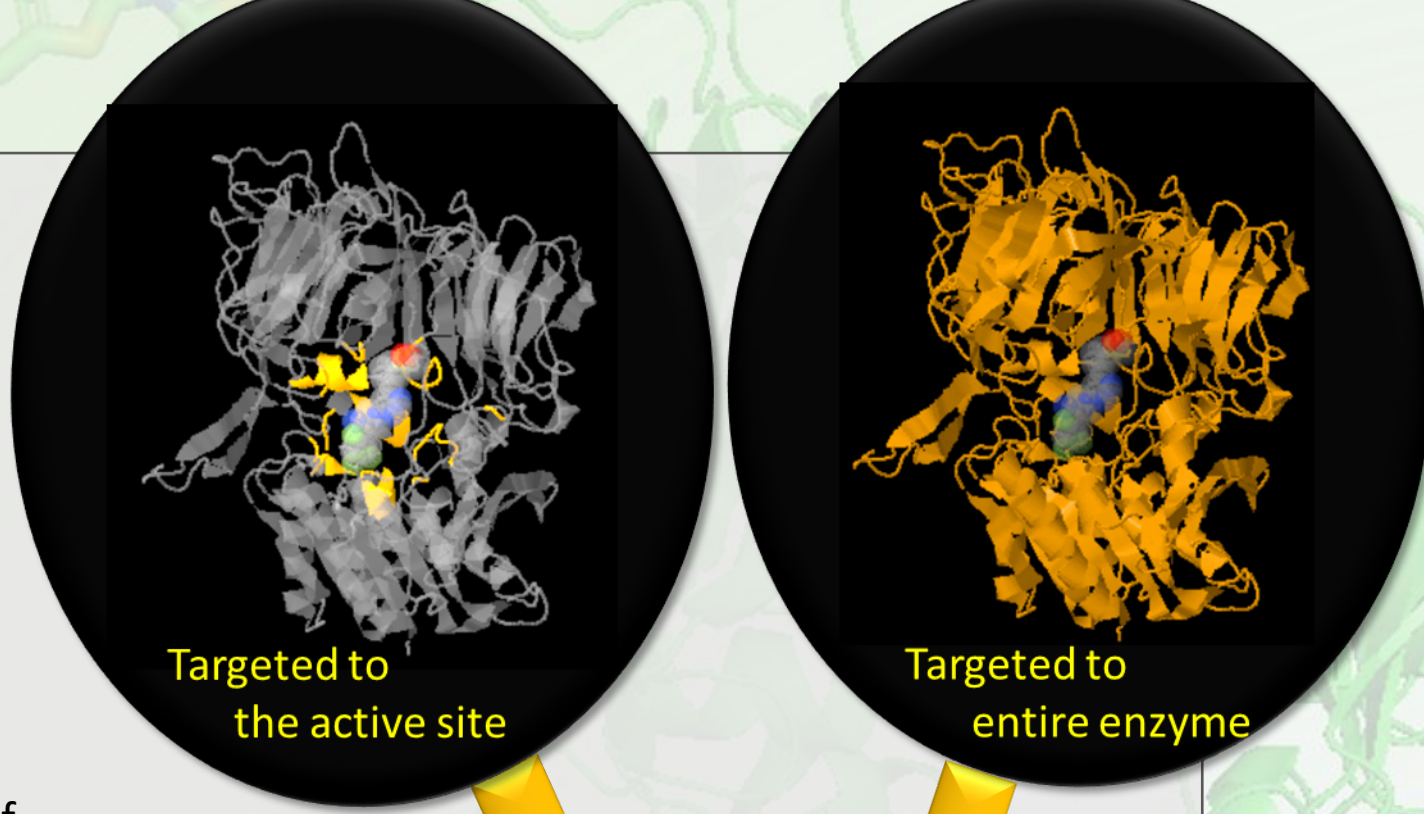


- No correlation between **in vitro calculated** IC_{50} values (or log IC_{50}) and the **in silico estimated** binding energy at the active site

Results:

- Probability Factor (PF)

we propose a probability factor (PF) that is extracted based on the combined results of docking analysis targeted at the active site of DPP4 and the entire enzyme.



$$PF = Est_{ts} - d,$$

$$d = \sum(\Delta Ex \cdot v_x/100) \cdot 10$$

$$\Delta Ex = Est\ x - Estt$$

Results:

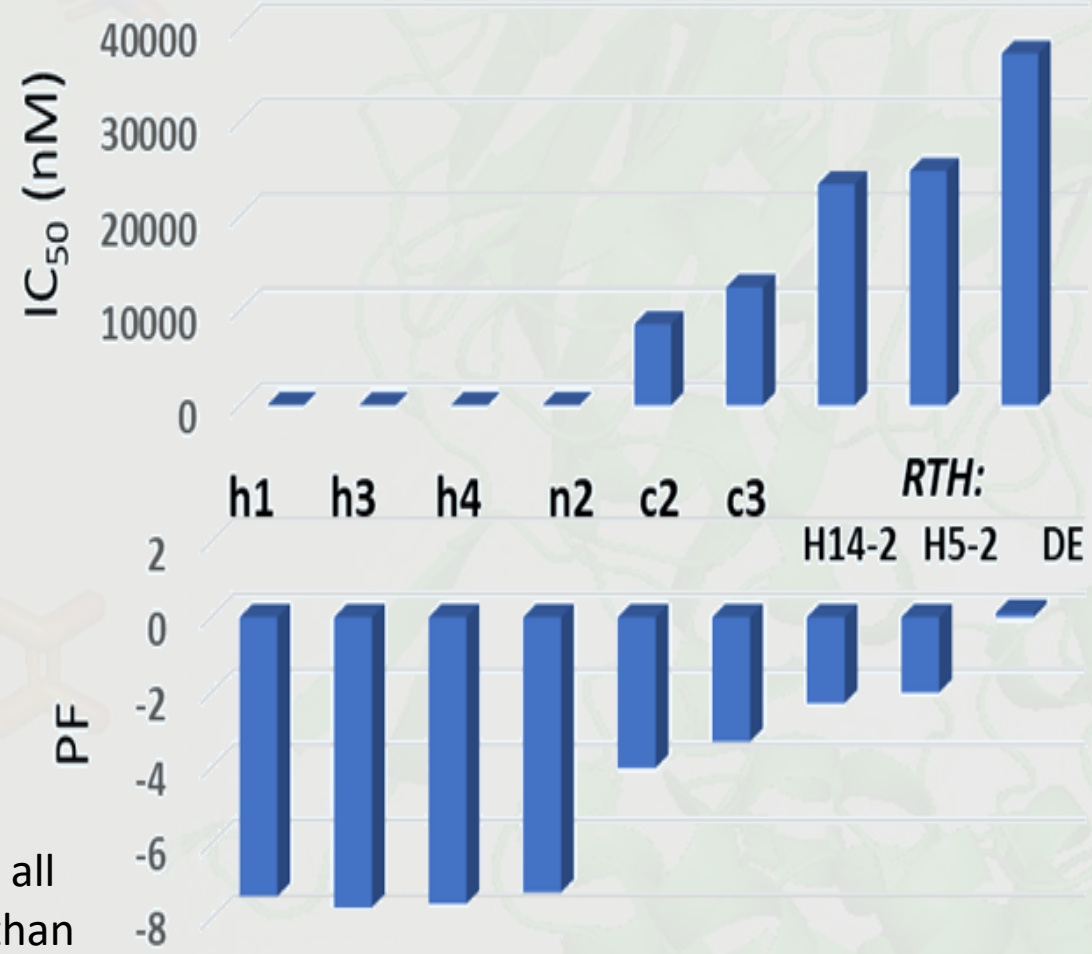
- Probability Factor (PF)

$$PF = Eest_{ts} - d,$$

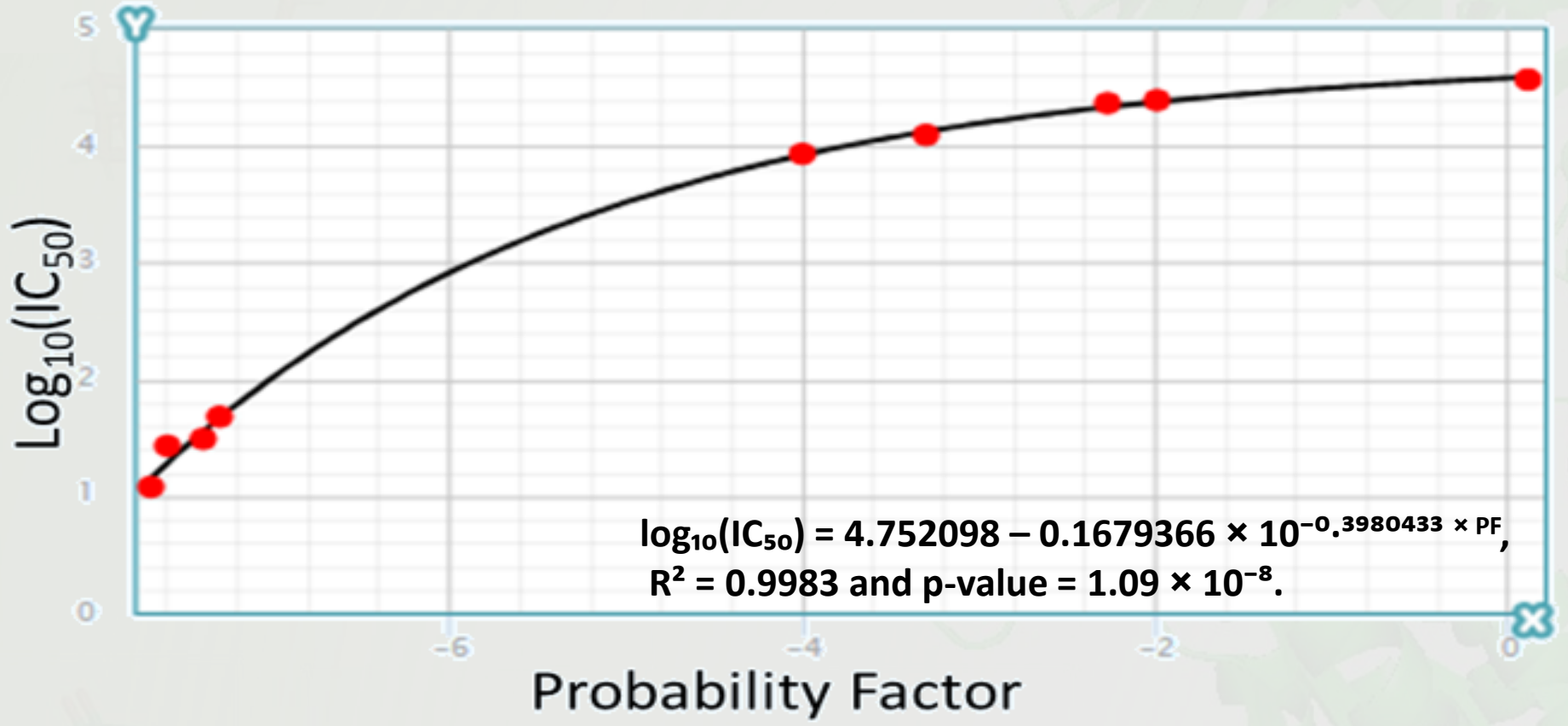
$$d = \sum(\Delta Ex \cdot v_x/100) \cdot 10$$

$$\Delta Ex = Eest\ x - Eestt$$

- Eest: Est. binding Energy, at target site (ts) and all positions (x)
- Vx: frequency (%) of the binding pose for all position with lower binding energy (Eest x) than that of the target site



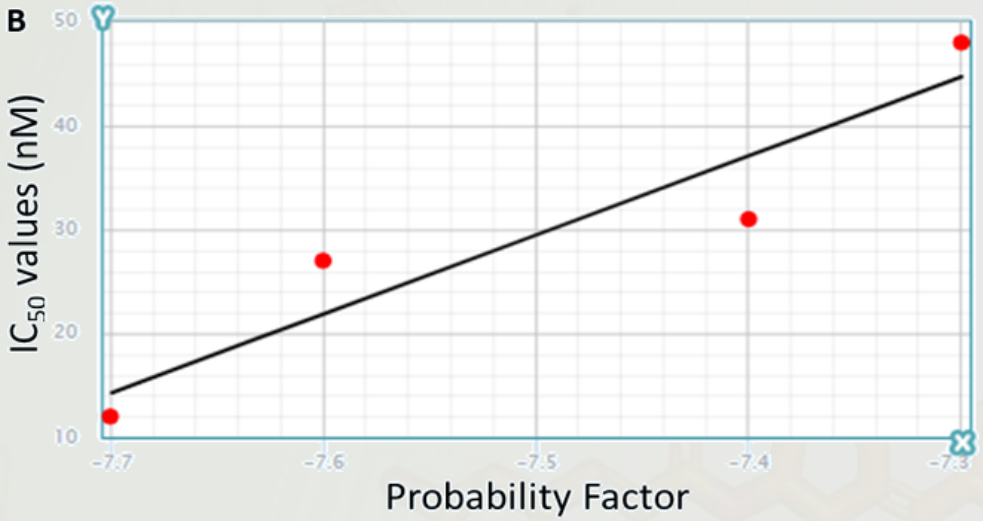
Results:

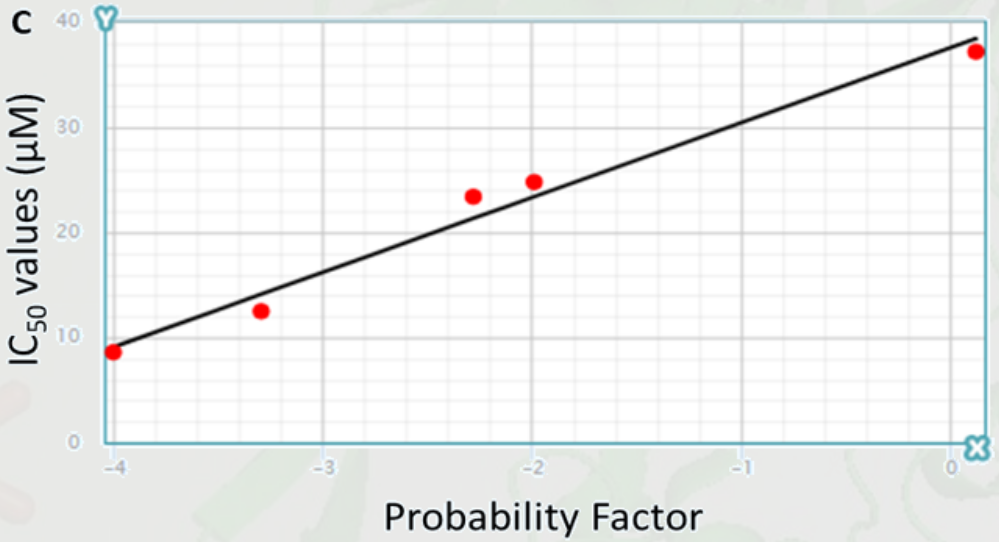

Log10(IC50)
5
4
3
2
1
0
-6
-4
-2
0
Probability Factor
log10(IC50) = 4.752098 – 0.1679366 × 10^−0.3980433 × PF,
R² = 0.9983 and p-value = 1.09 × 10^−8.

Results:

The **exponential curve** better describes the correlation **compared to the linear curve proposed previously** (Amanatidou, D., Eleftheriou Ph. etal. Pharmaceuticals 2025, 18, 52; https://doi.org/10.3390/ph18010052).

Results:





IC_{50} = 76 × PF + 599.5, with R^2 = 0.8791

IC_{50} = 7.1176 × PF + 37.611, with R^2 = 0.9794

- For practical purposes, a linear correlation between IC_{50} and PF can also be applied separately for the µM or nM range, which also shows relatively good R^2 values

Conclusions:

Probability Factor

- More accurate compound selection
- More reliable IC_{50} prediction.

Thank you for your attention