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Development of an empirical binding free energy model for phosphatidylinositol 4-kinase inhibitors

Natalie Mounteer Colodette (PG)1‡, Carlos Mauricio R. Sant'Anna (PQ)[1,2], Eliezer J. Barreiro (PQ)1*

[1]*LASSBio - Instituto de Ciências Biomédicas - UFRJ - CCS - Ilha do Fundão, Rio de Janeiro, RJ*
[2]*Departamento de Química, Instituto de Ciências Exatas, UFRRJ, Rodovia BR465, km 7, 23970-000, Seropédica, RJ*

‡**nm.colodette@gmail.com**
*__ejbarreiro@ccsdecania.ufrj.br__

Abstract: Kinases are proteins that have the function of transferring a γ-phosphate group of adenosine triphosphate (ATP) to hydroxyl groups of protein or lipid substrates, a process called phosphorylation [1]. One example is fosdatidylinositol 4-kinase (PI4K) responsible for phosphorylation at the 4-position of the inositol ring, thus forming the phosphatidylinositol 4-phosphate (PI4P) which regulates processes such as apoptosis, metabolism, cell growth and proliferation [4]. Due to its importance in physiological processes, PI4K is also related to the development of several diseases such as viral infections, cancers and neurological diseases [4]. Therefore, the search of new ligands for this enzyme may be of great therapeutic value and may also help to better understand the mechanisms of action by which the enzyme works. One of the ways to search for new ligands is to use *in silico* methods, where one can study the aspects involved in ligand-receptor interactions in detail and thus obtain proposed drugs with greater therapeutic advantages. Ki or IC_{50} values are constants that relate to the affinity of compounds for enzymes or receptors, and they are related to the free energy of binding (ΔG), which can be evaluated with empirical models by correlation with a series of energy terms theoretically obtained. Calculated parameters can be subjected to a multiple linear regression analysis to generate a model to predict the free energy and, therefore, the affinity of the compounds [6]. Based on the studies of Keaney and coworkers [7] eleven PI4KIIIβ-selective compounds (Figure 1) with IC_{50} ranging from 4 to 9727 nM were selected. All compounds had the energy minimized by the PM6 semi-empirical method after conformational analysis with the Spartan'16 program. The compounds were docked into the active site of the enzyme (crystallographic structure PDB: 4D0L) through the GOLD v. 5.5 program. The ChemPLP scoring function was used and the runs were made in triplicate, selecting the solutions with the best score. Calculations of the enthalpies of formation (ΔH_f) for complex, empty site and ligand were performed for each of the compounds with the PM7 semi-empirical method of the program MOPAC2016 and these data were used to obtain the interaction enthalpy ($\Delta H_{interaction}$) by the following equation:

$$\text{“}\Delta H_{interaction} = \Delta H_{f\ complex} - (\Delta H_{f\ protein} + \Delta H_{f\ ligand})\text{”}$$

Other information obtained included: the torsional energy ($E_{tors.}$) with the GOLD program and the solvation energy ($E_{solv.}$) with the Spartan'16 program. These parameters were combined in a multiple linear regression analysis by the OriginPro 2017 Student Version program to obtain a correlation function with the activity data (pIC_{50}). It was possible to obtain an optimal correlation with an adjusted R^2 of 0.895:

$$pIC_{50} = -0{,}05068\Delta H_{int.} + 0{,}36485E_{tors.} - 2{,}60214E_{solv.} - 0{,}04654E_{solv.}^2 + 32{,}84142$$

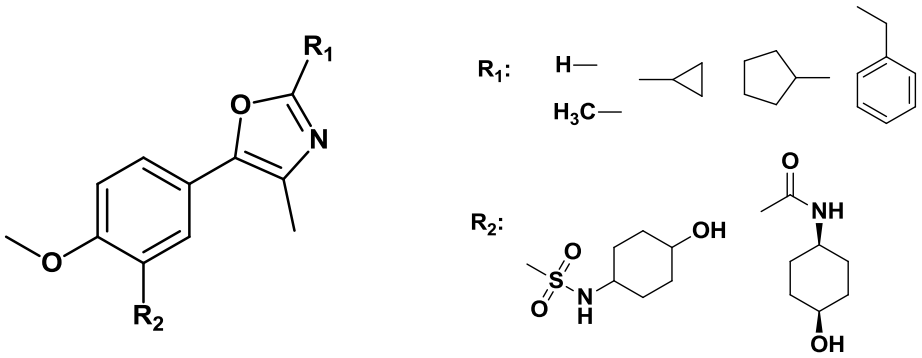

***Figure 1**: General structures of selected compounds*

Given the good results obtained for this initial series of PI4KIIIβ-selective compounds, new correlations involving a greater number of compounds and greater structural variability will be explored, seeking to obtain the most general activity prediction equation possible. This model will be useful to identify novel effective enzyme ligands in compound libraries and thus find new proposed PI4KIIIβ inhibitors.

Key-words: PI4KIIIβ, *In silico* methods, empirical binding free energy model.

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