PHYSICAL CHEMISTRY 2018

14th International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume I

September 24-28, 2018
Belgrade, Serbia

PHYSICAL CHEMISTRY 2018

14th International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume I

September 24-28, 2018
Belgrade, Serbia

ISBN 978-86-82475-36-1
Title: Physical Chemistry 2018 (Proceedings)
Editors: Željko Čupić and Slobodan Anić
Published by: Society of Physical Chemists of Serbia, Studentski Trg 12-16, 11158, Belgrade, Serbia
Publisher: Society of Physical Chemists of Serbia
For Publisher: S. Anić, President of Society of Physical Chemists of Serbia
Printed by: ″Jovan″, <Printing and Publishing Company, 200 Copies
Number og pages: 550+6, Format B5, printing finished in September 2018

Text and Layout: ″Jovan″

200 - *Copy printing*

3D MOLECULAR PHARMACOPHORE DETERMINATION OF PI3K-α KINASE INHIBITORS

Ž. Gagić [1], M. Jovanović [2], D. Agbaba [2] and K. Nikolić [2]

[1] Department of Pharmaceutical chemistry,Faculty of Medicine, University of Banja Luka, Save Mrkalja 14 , Banja Luka, Bosnia and Herzegovina.
[2]Department of Pharmaceutical chemistry,Faculty of Pharmacy, University of Belgrade,Vojvode Stepe 450, Belgrade, Serbia.
(katarina.nikolic@pharmacy.bg.ac.rs)

ABSTRACT

PI3K-α, as an enzyme with increased activity in many types of cancer, represents important target for research of new cytostatic agents. 3D-QSAR study was applied on 92 PI3K-α inhibitors in order to determine molecular pharmacophore structure. Obtained validation parameters (R^2=0.84; Q^2=0.67, R^2_{pred}=0.681) indicate on reliability and good predictive potential of the 3D-QSAR model. Pharmacophore analysis showed that following structural characteristic have the greatest impact on activity of PI3K-α inhibitors: presence of hydrogen bond donor and hydrogen bond acceptor at a distance of 18-18.4Å or 12-12.4Å, presence of hydrophobic domain and hydrogen bond donor at a distance of 15.2-15.6Å, presence of steric hot spot and hydrogen bond donor at a distance of 1.6-2Å and presence of hydrogen bond acceptor and steric hot spot at a distance of 14.4-14.8Å. These findings provide guidelines for future design of new PI3K-α inhibitors with enhanced activity.

INTRODUCTION

Phosphatidylinositide 3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate inositol phospholipids at the position 3 of inositol to give phosphatidylinositol 3,4,5-trisophosphate (PIP3). PIP3 leads to binding of PI3P binding proteins to plextrin homologous domains of cell membrane, including AKT serine/threonine kinase (protein kinase B or PKB) and 3-phosphatidylinositol-dependent kinase-1 protein (PDK1). AKT, when bound to the cell membrane, becomes active and phosphorylates several target molecules involved in cell survival, cycle, growth, motility and metabolismn[1].

PI3Ks are grouped into three classes, I, II and III, based on their structural characteristics and specificity for substrates. Class I is further divided into IA and IB. Class IA is a set of heterodimeric lipid kinases consisting of a p110

catalytic subunit and a p85 subunit that regulates receptor binding, activation and localization of PI3K enzymes. Mutations of one of the genes encoding primarily p110α subunit (PI3KCA) can be found in many types of human cancers, including brain, breast, colon, liver, stomach and ovarian cancers.

The aim of this research was to perform 3D-QSAR (3D-Quantitative Structure-Activity Relationship) study in order to define pharmacophore structure of the selective PI3K-α inhibitors that can be further used for design of new, more potent inhibitors.

EXPERIMENTAL

Experimentally determined Ki values of 92 PI3K-α inhibitors were collected from ChEMBL database (https://www.ebi.ac.uk/chembl/) and expressed as pKi (-logKi) [2-5]. Wide range of inhibitory activities (pKi: 4.5-10.5) was covered, which enabled the formation of a robust 3D-QSAR model with a broad applicability domain. For each compound were checked dominant forms at pH=7.4 in MarvinView 17.28 program. Energy minimization of molecular structures was performed with PM3 semi-empirical and then *ab initio* Hartree-Fock/3-21G method using Gaussian 98W program included in Chem3D Ultra 7.0 software package.

3D-QSAR model was created in Pentacle 1.07 using the GRIND (GRid-Independent) descriptors, derived from molecular interaction fields- MIFs. To calculate these descriptors program uses 4 chemical probes which simulate the interaction of the ligand with the active site of receptor: DRY probe represents a hydrophobic interaction, O probe (carbonyl oxygen) describes the hydrogen bond acceptor, N1 (amide nitrogen) represents the donor of the hydrogen bond, and the TIP probe describes the steric hot spot. The most important regions that represent favorable interactions between probe and ligand are extracted using ALMOND algorithm based on two criteria: the intensity of the field and the distance between the selected probes. For field encoding, the CLACC (Consistently Large Auto and Cross Correlation) methodology was used. 3D-QSAR model was formed using PLS (Partial Least Square) regression.

RESULTS AND DISCUSSION

Dataset of 92 molecules is divided into a training set (62 molecules) and a test set (30 molecules). Using the training set, a PLS (Partial Least Squares) regression model was created with 2 latent variables and internal validation parameters: R^2=0.84; Q^2=0.67; SDEP=0.442. For an acceptable QSAR model value of R^2 (coefficient of determination, measures how well the regression line actually fits the data) should be greater than 0.6 and value of Q^2 (cross-validated coefficient of determination) should be greater than 0.5. The test set

was used for external validation and the following parameters were obtained: R^2_{pred}=0.681; SDEP=0.567; r^2_m=0.594; $\overline{r^2_m}$ =0.594; Δr^2_m=0.0004. These values indicate on the good reliability of the prediction of the created 3D-QSAR model that was further used to analyze 3D pharmacophore structure of PI3K inhibitors.

The variables with the highest positive effect on activity are depicted on 3D structure of the most active compound from dataset (Fig. 1). Var 647 and 632 (O-N1) are formed between nitrogen from triazole as the acceptor of hydrogen bond and nitrogen from the amide functional group as the donor of hydrogen bond; Var 382 (DRY-O) is formed between 1,2,4-triazole as a hydrophobic group and nitrogen amide as a donor of a hydrogen bond; Var 692 (O-TIP) is formed between nitrogen from the amide functional group and hydrogen related to this nitrogen (steric hot spot); Var 810 (N1-TIP) is formed between oxygen as the acceptor of hydrogen bond and the isopropyl ring as a steric hot spot.

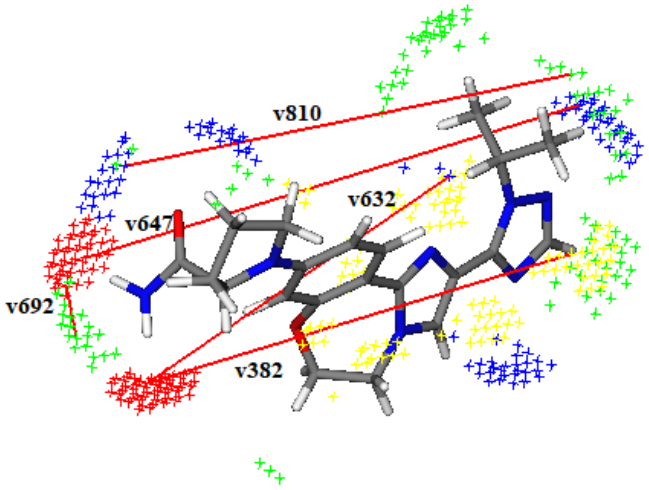

Figure 1. 3D structure of the most active compound from data set (pKi=9.873) with favorable variables depicted in red lines

The variables with the highest negative effect on activity are depicted on 3D structure of the least active compound from dataset (Fig. 2). Var 268 and 270 (TIP-TIP) are formed between oxygen from the amide and methyl group as steric hot spots; Var 724 (O-TIP) is formed between the nitrogen from the amide (hydrogen bond donor) and hydrogen from a pyrimidine (steric hot spot); Var 703 (O-TIP) is formed between the nitrogen from the amide (hydrogen bond donor) and oxygen from the amide (steric hot spot); Var 468

(DRY-N1) is formed between oxygen from the amide as a hydrogen bond acceptor and pyrimidine as a hydrophobic structure.

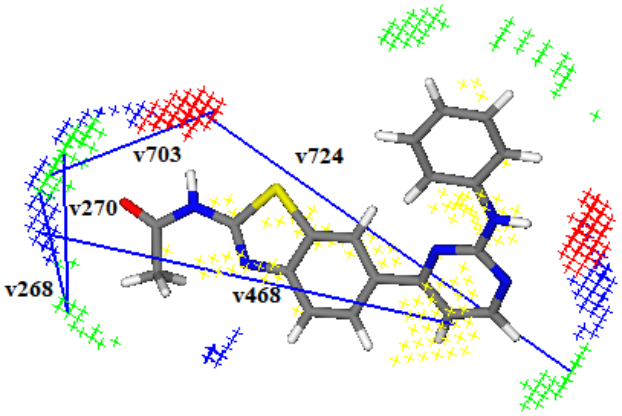

Figure 2. 3D structure of the least active compound from data set (pKi=6.970) with unfavorable variables depicted in blue lines

CONCLUSION

Created 3D-QSAR model can reliably be used for PI3K activity prediction of new compounds within the applicability domain. The most important structural characteristics that have positive and negative impact on activity were identified and will be used for design of new PI3K inhibitors.

Acknowledgement

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant # 172033).

REFERENCES

[1] C. Huang, D. Mandelker, S. B. Gabelli, L. M. Amzel, Cell Cycle, 2008, 7(9), 1151-1156.
[2] T. P. Heffron et al, Journal of Medicinal Chemistry, 2016, 59, 985-1002.
[3] T. P. Heffron et al, ACS Medicinal Chemistry Letters, 2016, 7, 351-356.
[4] N. D. D'Angelo et al, Journal of Medicinal Chemistry, 2011, 54(6), 1789-1811.
[5] P. N. Collier et al, Journal of Medicinal Chemistry, 2014, 58, 517-521.