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A 3D-QSAR STUDY ON A SET OF MAPK1 INHIBITORS

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ABSTRACT
Three different classes of mitogen-activated protein kinase 1 (*MAPK1*) inhibitors (derivatives of pyrimidine-pyridone, acetamidothiazole and pyrazolyl-pyrrole) were used to perform three-dimensional Quantitative Structure-Activity Relationship (*3D-QSAR*) study. The number of 92 *MAPK1* inhibitors, split into training and test sets, was extracted from ChEMBL database, with their enzymatic inhibitory constants determined on human *MAPK1*. The statistically significant *3D-QSAR* models were further validated. The 3D-QSAR model with the best statistical and validation parameters was further used to define main structural determinant for efficient inhibition of MAPK1 enzyme.

INTRODUCTION
Today, 42 kinase inhibitors [1] have been FDA approved. Mitogen-activated protein kinase 1 (*MAPK1*) presents serine-threonine kinase which is included in *Ras/Raf/MEK/MAPK* signaling pathway [2]. Cancer cells found in pancreas, colon, lungs, ovaries and kidneys may have overexpressed *MAPK1* level [3], which makes this enzyme as an attractive molecular target for the development of novel *MAPK1* inhibitors. So far, there are no registered *MAPK1* inhibitors, thus any new drug design strategy in this field is kindly welcomed. This communication deals with the developing 3D-QSAR model and consequently analysis of GRIND variables related to developed model.

EXPERIMENTAL
Diverse 92 compounds with experimentally determined enzymatic inhibitory constants *Ki* against human MAPK1 isoform were downloaded from ChEMBL database (https://www.ebi.ac.uk/chembl/). The data set is composed of three different classes of compounds (derivatives of pyrimidine-pyridone, acetamidothiazole and pyrazolyl-pyrrole), with the pKi range 4.86-10. The dominant forms at the physiological *pH*=7.4 were determined by use of Marvin Sketch software, version 5.5.1.0 [4]. The conformations of the

molecules were generated by Chem3D Ultra 7.0 software (Hartree-Fock 3-21G method) [5].

Pentacle Software 1.07 [6] derived the GRIND descriptors for prepared compounds. The software uses four different molecular probes (*DRY* - hydrophobic, *TIP* - molecular shape, *N1* – hydrogen bond accepting (HBA) and *O* – hydrogen bond donating (HBD) interactions), imitating the most important interactions between the examined compounds and the amino acids residues inside the receptor binding cavity. The GRIND descriptors are derived between two probes on a certain distance, thereby correlated with the *pKi* values of the modelled compounds, by using Partial Least Squares (PLS) regression.

In order to develop 3D-QSAR model, the total number of compounds was divided into two data sets – training (composed of 62 compounds) and test set (30 compounds). The training set compounds were chosen according to the Principal Component Analysis (PCA), regarding the principle that the test set compounds remained adjacent at least one of the training set compound. The total number of GRIND variables was reduced by Fractional Factorial Design, whereas the most significant were retained and used for structure-activity relationship description. The validity of the developed 3D-QSAR model was evaluated through calculation of internal and external validation parameters [7].

RESULTS AND DISCUSSION

The results of the developed 3D-QSAR model are presented in **Table 1**.

Table 1. Validation parameters for the developed *3D-QSAR* model

	Internal validation		
Parameter	$\mathbf{R^2}$	$\mathbf{Q^2_{LOO}}$	**RMSEE**
	0.900	0.780	0.479
Criteria	> 0.7	> 0.5	

	External validation							
Parameter	$\mathbf{R^2_{pred}}$	$\mathbf{R^2_{obs/pred}}$	**RMSEP**	$\mathbf{r_m^2}$	$\mathbf{r_m^{/2}}$	$\mathbf{\Delta r_m^2}$	$\mathbf{\overline{r_m^2}}$	***k***
	0,677	0.900	0,871	0,625	0,499	0,126	0,562	0,988
Criteria	> 0.6		≤ 2RMSEE	> 0.5	> 0.5	< 0.2	> 0.5	0.85≤ k ≤1.15

R^2 - *coefficient of determination*, **Q^2_{LOO}** - *Leave-One-Out Cross-Validated squared correlation coefficient*, **RMSEE** - *Root Mean Square Error of Estimation*, **RMSEP** - *Root Mean Square Error of Prediction*, ***r^2_m metrics*** (r^2_m, r'^2_m, $\overline{r^2_m}$ and Δr^2_m)

The 3D-QSAR model developed by using standard chemometric approaches (PCA and PLS regression) defined valid, three-component

(LV=3) model (the validity and accuracy are presented in **Table 1**). The most significant GRIND variables correlating with the MAPK1 inhibitory activity of the modelled compounds belong to classes of **TIP-TIP**, **DRY-TIP**, **O-TIP** and **N1-TIP** GRIND descriptors (**Figure 1**).

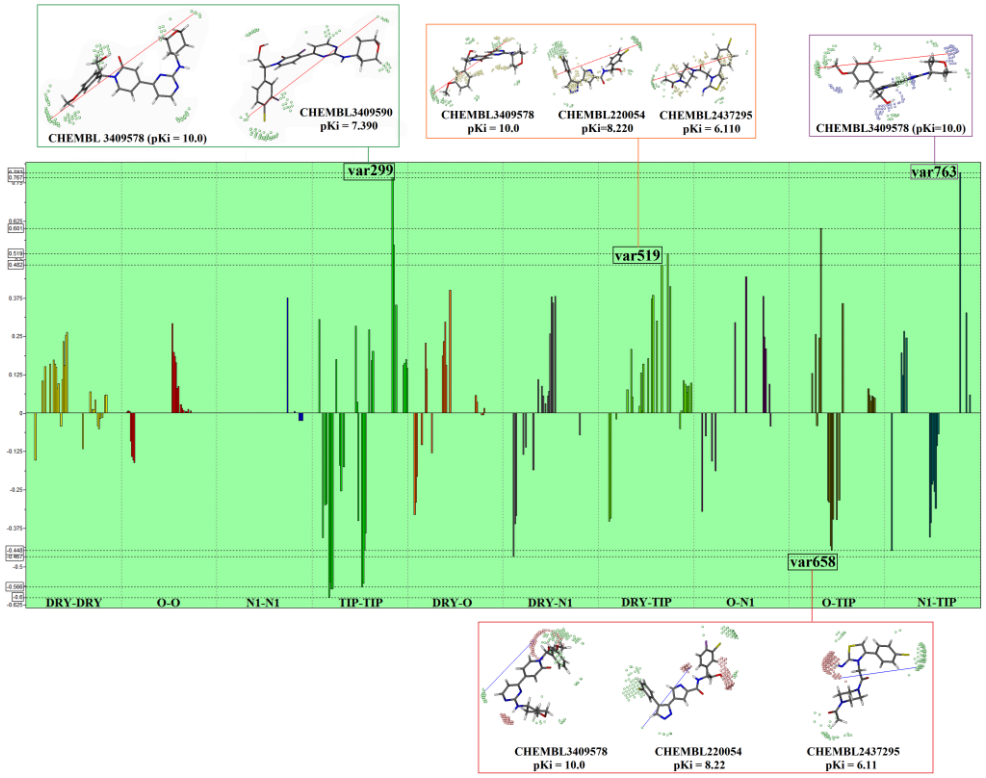

Figure 1. PLS coefficient plot presented for MAPK1 *3D-QSAR* model along with most significant GRIND variables (upper corner, positively correlating var299, var519 and var763 with *pKi* and below – negatively correlating var658 with *pKi*)

TIP-TIP var299 has the largest positive influence on the *pKi* only in the highly potent MAPK1 inhibitors, such as pyrimidine-pyridones (pKi =7.39 – 10.0). It implies that the molecular shape of these inhibitors is complementary to the binding pocket of MAPK1. This variable possesses discriminative property between pyrimidine-pyridones and two other classes of examined MAPK1 inhibitors. GRIND variable 519 (**DRY-TIP**) illustrates the importance of hydrophobic interactions of tetrahydropyran moiety in the MAPK1 inhibitors, as it is consistently pronounced in all the compounds with the same type of ring.

The GRIND variable **N1-TIP** (var763) is presented between steric spot interacting with distal methoxy group attached to pyrimidine-pyridone scaffold and oxygen (HBA group) from tetrahydropyran ring interacting with **N1** probe. This variable is presented on a distance of 24.4-24.8 Å and uniquely existing in pyrimidine-pyridone derivatives.

Finally, the most prominent variable with negative influence on *pKi* value is **O-TIP** var658. It is positioned between steric spots described around heterocyclic ring and ***O*** probe interacting with amide hydrogen in pyrazolyl-pyrroles. This variable has the largest values in moderate and less potent MAPK1 inhibitors (pKi < 7.460), comparing to the most potent pyrimidine-pyridone derivatives, indicating that 13.6-14 Å is not optimal distance between HBD group and distal heterocycle for efficient MAPK1 inhibitions.

CONCLUSION

The GRIND analysis within developed MAPK1 *3D-QSAR* model revealed structural motifs which are important for potency against MAPK1. The validity of the model was confirmed by internal and external validation. The most significant variables (var299, var519, var763 and var658) were successfully applied to define the differences in biological activity of pyrimidine-pyridone, acetamidothiazole and pyrazolyl-pyrrole derivatives, as MAPK1 inhibitors.

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