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3D-QSAR STUDY OF PYRAZOLO[3,4-d]PYRIMIDINES AND 1,3,4-THIADIAZOLES AS BCR-ABL1 INHIBITORS

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ABSTRACT

The treatment of chronic myeloid leukemia (CML) was revolutionized by introducing Bcr-Abl1 inhibitors to the extent that today it could be considered as manageable chronic disease. Although, ATP-competitive Bcr-Abl1 inhibitors set the milestone for treatment of CML, resistance on therapy in significant number of patients still remains major challenge.

3D quantitative structure-activity relationship (3D-QSAR) model of selected Bcr-Abl1 inhibitors was built in order to gain insight into structural requirements for inhibitory activity. The 3D-QSAR model with best validation parameters was selected for further study and design of novel inhibitors.

INTRODUCTION

Reciprocal translocation between chromosomes 9 and 22, known as Philadelphia chromosome, results in the expression of constitutively activated fused Bcr-Abl1 protein kinase which has the central role in the pathogenesis of chronic myeloid leukemia (CML). Owing to ATP competitive Bcr-Abl1 inhibitors, CML could be considered as chronic disease today. However, development of resistance on therapy with known drugs, especially in the advanced phases of CML, is the major driving force for development of novel inhibitors [1].

During more than 20 years of quest for effective and safe Bcr-Abl1 inhibitors, pyrazolo[3,4-d]pyrimidine and 1,3,4-thiadiazole scaffolds, as privileged fragments in medicinal chemistry and bioisosteres of nucleobases, emerged as some of the most promising fragments for the development of novel generations of inhibitors. Recent reports revealed potential of these compounds in overcoming resistance, even achieving additional allosteric binding sites which could have further positive implications in therapy of resistant patients [2].

The aim of the current study was to generate three dimensional quantitative structure activity relationship (3D-QSAR) model based on alignment-

independent GRIND descriptors calculated for selected pyrazolo[3,4-d]pyrimidine and 1,3,4-thiadiazole Bcr-Abl1 inhibitors in order to identify 3D structural features important for the interaction and to set additional guidance for design of novel Bcr-Abl1 inhibitors.

EXPERIMENTAL

Activities expressed as pK_i and structures of Bcr-Abl1 inhibitors have been obtained from ChEMBL database (https://www.ebi.ac.uk/chembl/). Total of 107 inhibitors with pyrazolo[3,4-d]pyrimidine and 1,3,4-thiadiazole scaffolds (Figure 1) tested with the same biological assay were extracted for further analysis. Major microspecies at physiological pH were obtained with Marvin Suite [3]. The Gaussian 98 [4] software with Hartree-Fock/3-21G basis set was applied for geometry optimization. Pentacle software [5] was used for further processing of structures and 3D-QSAR model building and validation.

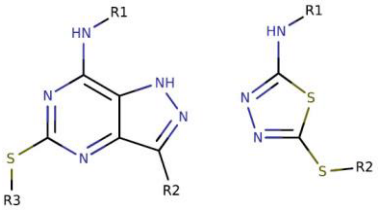

Figure 1. Representation of structures in data set. R1 and R2 represent phenyl containing groups while R3 is aliphatic group.

Pentacle generates molecular interaction fields (MIFs) for each optimized ligand using four GRID-based fields calculating interaction energies between ligands and probes: DRY-hydrophobic reactions, N1-hydrogen bond acceptors, O-hydrogen bond donors and TIP-steric hot spots within molecule. The interaction energies at each grid point called node are the sum of Lennard-Jones energy, hydrogen bond, and electrostatic interactions. ALMOND algorithm was used to extract the most relevant MIF regions. Encoding of extracted MIFs into alignment independent GRIND (GRid-Independent) descriptors was performed by means of CLACC algorithm. Principal component analysis (PCA) was used for inspection of structural variance of initial data set. After dividing data set into test and training set and fractional factorial design with enhanced replacement method (FFD) for selection of representative GRIND variables from initial pool of descriptors, partial last square regression (PLS) was used for model generation. Internal validation of developed model was evaluated using coefficient of determination (R^2), leave-one-out cross-validated coefficient of determination (Q^2), root mean square error of estimation (RMSEE). External validation was performed calculating coefficient of determination for test set (R^2_{pred}), root meant square error of prediction (RMSEP) and r^2_m metric parameters.

RESULTS AND DISCUSSION

Structural variance of initial data set was examined with PCA performed on whole set of GRIND variables. Based on PCA score vectors, outliers were detected and eliminated from initial data set. Remained total of 90 compounds were randomly divided into test and training set. Partial last square regression (PLS) was used for 3D-QSAR model building. Four latent variables (LVs) were selected as optimum number of PLS components for the model interpretation. Validation parameters obtained by leave-one-out cross validation and external validation with test set, indicated excellent quality and justify usage of 4LV 3D-QSAR model in further design of novel Bcr-Abl1 inhibitors (Table 1).

Table 1. Validation parameters for selected 3D-QSAR model (4LV).

R^2	Q^2	RMSEE	R^2_{pred}	RMSEP	r^2_m	
					$\bar{r}^2_m$	Δr^2_m
0.920	0.700	0.240	0.672	0.210	<0,2	>0,5

4LV PLS coefficients plot (Figure 2A) indicate GRIND variables: var 246 (-TIP-TIP/8,4-8,8Å), var 263(+TIP-TIP/16,2-15,6Å), var 315 (+DRY-O/6-6,4Å), var 401 (+DRY-N1/10,4-10,8Å), var 640 (+O-TIP/16-16.4Å) and var 687 (-N1-TIP/4,8-5,2Å) as the most important for the activity.

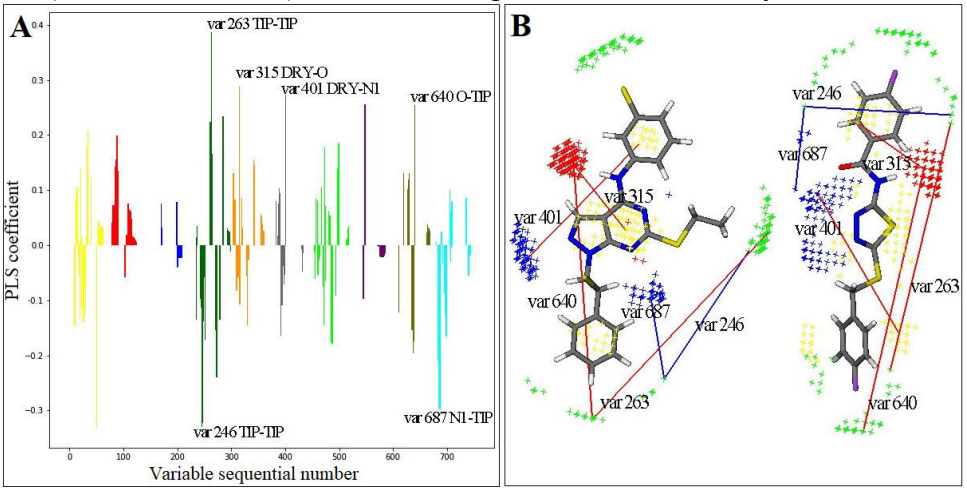

Figure 2. A 4LV PLS coefficients plot for obtained model with the most significant variables labeled. **B** Pyrazolo[3,4-d]pyrimidine (left) and 1,3,4-thiadiazole (right) derivatives with selected GRIND variables (GRID based fields: TIP-green, DRY-yellow, O-red, N1-blue).

Var 246 (-TIP-TIP) and var 263 (+TIP-TIP) are describing the distance between two steric hot spots that has negative and positive impact on activity, respectively. These variables are related to optimal substitution of phenyl

moieties in both groups of inhibitors. In the group of pyrazolo[3,4-d]pyrimidines, these variables strongly support substitution in *–p* position of phenethyl group with voluminous substituents, while in the group of 1,3,4-thiadiazole describe the optimal distance between two opposite sides of molecules indicating that changing the length of linkers will have negative impact on activity. Var 315 (+DRY-O), var 401 (+DRY-N1) ,var 640 (+O-TIP) and var 687 (-N1-TIP) clearly indicates importance of hydrogen bond donors and acceptors in central scaffold and their optimal distance form steric and hydrophobic hot spots (Figure 2B).

According to developed 3D-QSAR models, we suggest that a more potent inhibitor against Bcr-Abl1 might be obtained by (i) increasing hydrogen bonding strength in central scaffold; (ii) optimal substitution of phenyl groups which increases hydrophobicity of favorable region and maintains optimal distance between described steric hot spots (iii) preserving optimal lengths of linkers in 1,3,4-thiadiazole and by introducing bulky substituent into *–p* position of phenethyl group of pyrazolo[3,4-d]pyrimidines.

CONCLUSION

In summary, an alignment-independent QSAR study was performed on a set of pyrazolo[3,4-d]pyrimidine and 1,3,4-thidiazole derivatives with Bcr-Abl1 inhibitor activity. Model with good statistic was developed and structural properties important for activity were described. The 3D-QSAR model could be further used for design of novel series of Bcr-Abl1 inhibitors.

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