

Research Article

3D QSAR STUDIES OF PYRROLO[2,1-F][1,2,4] TRIAZINES AS TYROSINE KINASE INHIBITORS

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ABSTRACT

Recently several pyrrolo triazine derivatives were identified as potentially active anticancer agents against vascular endothelial growth factor receptor (VEGFR) tyrosine kinases. 3D QSAR studies for the 10 molecules of various substituted pyrrolo[2,1-f][1,2,4] triazines by using k-Nearest Neighbor Molecular Field Analysis (kNN-MFA) combined with various selection procedures was performed. Using kNN-MFA approach 14 3D-QSAR models were generated; one of these models was selected on the basis of q^2 and pred_r^2 values. The selected model had shown good internal and external predictivity for the training set of 7 molecules and test set of 3 molecules with validation (q^2) and cross validation (pred_r^2) values of 0.9945 & 0.2096 respectively.

Keywords: Pyrrolo triazine, 3D QSAR, kNN-MFA, Anticancer

INTRODUCTION

Tumor invasion and metastasis are the major causes of treatment failure and death in cancer patients. About 30% of patients with newly diagnosed tumors already have detectable metastases. Of the remaining 70% who are clinically free of metastasis, about half of them develop metastatic spread during follow-up after a potentially radical treatment of primary tumor¹. Cancer drug therapy is undergoing a major transition from the previous pregenomic cytotoxic era to the new post genomic era. New cancer drug targets are identified and validated in various ways. The determination of the normal human genome sequence, followed by that of multiple cancer genomes, is accelerating target discovery².

Depending on the mode of action and the specific "targets", various agents are identified. Tyrosine Kinase Inhibitors are one of them³. Tyrosine kinase plays an important role in angiogenesis and neovascularization. This process though occurs normally during embryonic development, female reproductive cycle or wound healing is found as a crucial step in tumor transition from benign to malignant form, capable of spreading throughout the body⁴. Targeting receptor protein tyrosine kinases (RPTKs) as cancer chemotherapy has continued to become a compelling approach with time. The advances in our understanding of the oncogenic activation of these receptors have been matched by the identification of new structural classes of kinase inhibitors with improved potency, specificity and efficacy⁷.

The computer-aided prediction of biological activity in relation to the chemical structure of a compound is now a commonly used technique in drug discovery⁸⁻¹¹. Using high-resolution data on enzymes, computer-based approaches help identify or design ligand that possesses good steric and chemical complementarities to various sites in the macromolecular target. This process is often referred to as "structure-based design"¹². In the present investigation efforts were to relate the dependence of the anticancer activity of new compounds on the nature of substitution in the

pyrrolo triazine analogues. The present 3D QSAR study was carried out by using k-Nearest Neighbor Molecular Field Analysis (K-NNMFA) method for predicting the anticancer activity. The results obtained from this study would be useful in both understanding the favorable and non-favorable contours as well as in rapidly and accurately predicting the activities of designed inhibitors. These models also provide some beneficial clues in structural modification for designing new inhibitors for the treatment of cancer with much improved inhibitory activities against tyrosine kinase activity.

MATERIAL AND METHODS

The in vitro percentage inhibition values for tyrosine kinases of Pyrrolo[2,1-f][1,2,4] triazine analogues against vascular endothelial growth factor receptor were taken from the literature¹³. To these values, one of the modest kNN-MFA with various variable selection methods was applied. Similar to many 3D QSAR methods¹⁴⁻¹⁵ kNN-MFA requires suitable alignment of set of molecule. This is followed by generation of common rectangular grid around the molecules. The steric and electrostatic energies are computed at the lattice point of grid using methyl probe of charge +1, these interaction energy values at the grid point are considered for relationship generation using kNN method and utilized as descriptors to decide nearness between molecules¹⁶.

All the 10 molecules taken in the study (Fig.1) were drawn in Vlife QSAR Plus software. They were optimized by using "Merck Molecular Force Field (MMFF)" and they were batch optimized also (as described in table.1). After this all the 10 molecules were aligned (Fig.2) using template based alignment method by choosing a minimum common structure as "Template" (Fig.3) and the most effective one as the 'Reference Molecule' (Fig.4). From the 10 molecules taken in the study, a training set of 7 molecules & test set of 3 molecules were generated using the various selection procedures. After the selection of the test and training sets, kNN methodology was applied to the descriptors generated over the grid as shown in the 'Show Point' (Fig.5).



Fig.1: Structures of the molecules for the series

Table 1: List of substituents for the series

Compound	R ¹	R ²	R ³	IC ₅₀ (μ m)
1	CH ₃	CH ₃	H	>2
2	H	H	H	>10
3	CH ₃	H	H	>10
4	H	CH ₃	H	>2
5	H	H	CH ₃	>2
6	H	H	H	1.44 \pm 0.95
7	CH ₃	H	H	0.066
8	H	CH ₃	H	0.405
9	H	H	CH ₃	>10
10	CH ₃	CH ₃	H	0.023

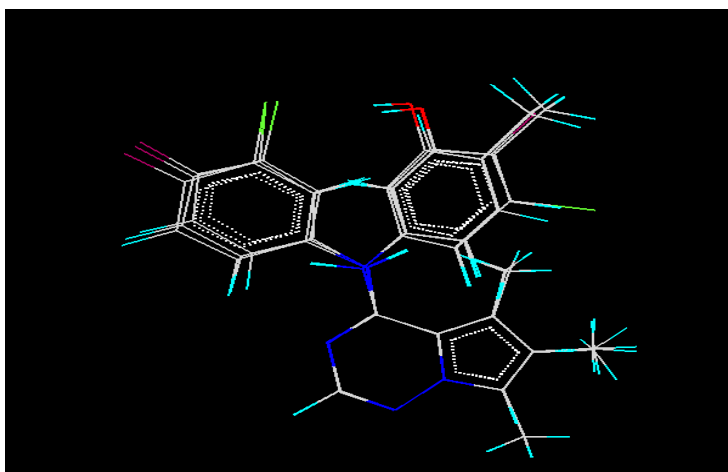


Fig.2: Aligned molecules of the series

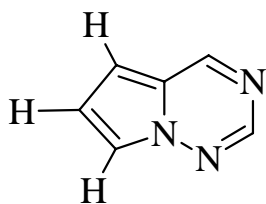


Fig. 3: Template

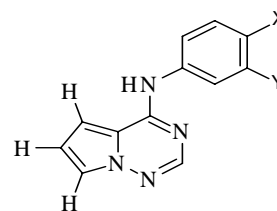


Fig.4: Reference Molecule

Table 2: Model summary

Training Set
Size = 6,

Test Set Size =
3

**Selected
Descriptors:**

E_6, E_313

Statistics:

k Nearest
Neighbour= 1

RESULTS AND DISCUSSION

The importance and utility of the new 3D QSAR method discussed has been established by applying it to known sets of molecules as described above. We report that 14, 3D QSAR models were generated by kNN-MFA in conjunction with Simulated Annealing (SA), Genetic Algorithms & Stepwise (SW) Forward Backward selection method. From these models, two of them were having good q^2 & pred_r^2 values, one of which was selected having good internal & external predictivity. For this model training and test sets were

selected using random selection method and the descriptors were selected using simulated annealing method. The summary of the selected model is given in Table.2

EVALUATION OF QSAR MODELS

The QSAR models were evaluated using following statistical measures: n-number of descriptors; k-number of nearest neighbors; q^2 - cross validated r^2 (by leave-one-out method); pred_r^2 - predicted r^2 for the external test.

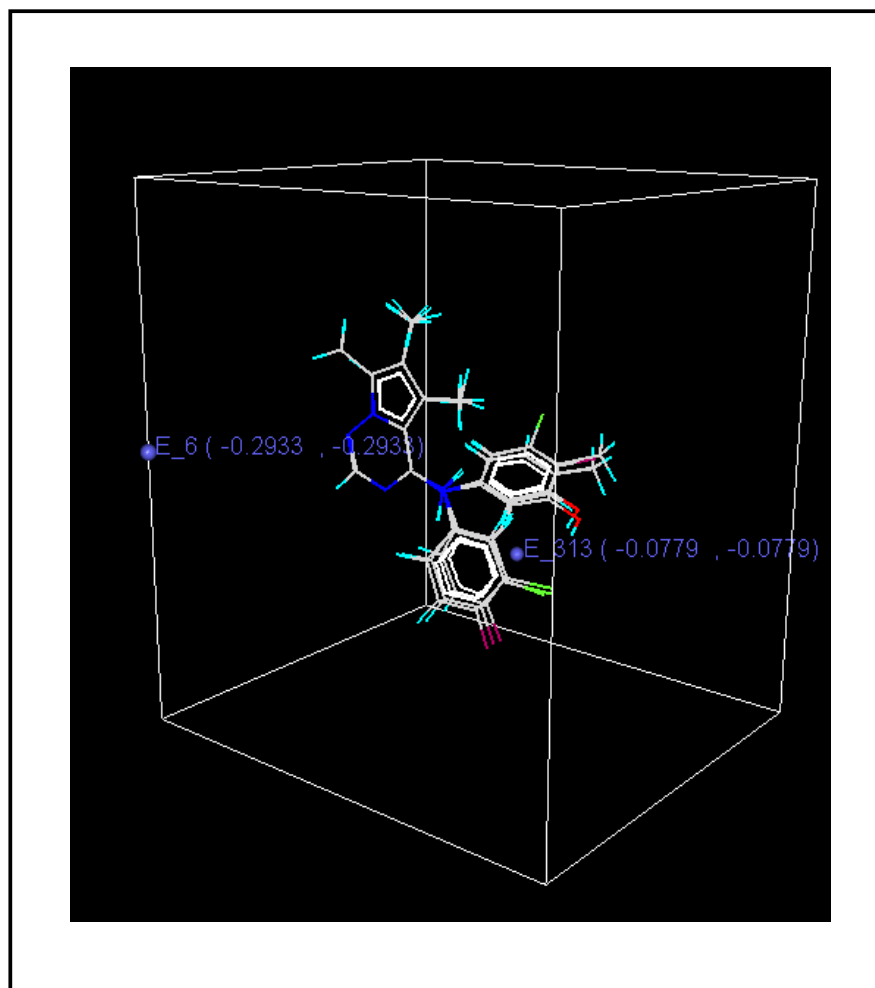


Fig.5: Show point

CONCLUSION

The selected model has shown good internal and external predictivity with $q^2=0.9945$ and $\text{pred}_r^2= 0.2096$ for the training and test set molecules. The presence of electronegative groups on molecule with less bulky substituents on other positions has shown better activity. Thus, it would be worthwhile to synthesize a novel pyrrolo[2,1-f][1,2,4] triazines with less bulky groups and more electronegative groups on benzene ring.

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