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ORIGINAL ARTICLE

Pharmacophore mapping: Prediction of BCR–ABL kinase inhibitory activity of α-benzylthio chalcones

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Abstract In this investigation, 3D pharmacophore modeling studies were performed on a diverse set of 33 α-benzylthio chalcone derivatives that demonstrate anticancer activity by blocking BCR–ABL phosphorylation in leukemic cells. Pharmacophore modeling is based on the principle of the alignment of pharmacophoric features which has been carried out on the same set of molecules. Five point pharmacophores with one negative ionizable group, one hydrophobic group and three aromatic rings as pharmacophoric features were developed. Pharmacophore hypothesis HNRRR 1501 yielded a statistically significant 3D-QSAR model with R^2 value 0.9103 and was considered to be the best pharmacophore hypothesis. The selected pharmacophore model HNRRR 1501 was externally validated by predicting the activity of test set. The correlation coefficient of 0.8856 was observed between experimental and predicted activities of test set. The features of pharmacophore were expected to be useful for the design of selective BCR–ABL tyrosine kinase inhibitors.

1. Introduction

Chronic myelogenous leukemia (CML) is a slow growing cancer where white blood cells are produced in excess by bone marrow.[1] In Chronic myelogenous leukemia patients, the reciprocal translocation between the long arms of chromosomes 9 and 22, results in the Philadelphia (Ph1) chromosome.[2,3] As evident from *in vitro* and *in vivo* studies, it has been established that the tyrosine kinase activity of the BCR–ABL is sufficient to cause CML,[4–7] which makes BCR–ABL tyrosine kinase inhibitors as the first line therapy for CML.[8] BCR–ABL tyrosine kinase inhibitors inhibit the expression of specific target genes that contribute to the malignant transformation of Philadelphia positive cells.[9]

Traditional natural products have cancer preventing properties.[10] In a recent review, Sharma et al. described the potential of heterocyclic chalcone analogs as potential anticancer agents.[11] The effectiveness of chalcone derivatives in different cancers is proved by various researchers from time to time i.e. leukemia, colorectal adenocarcinoma, melanoma,[12] cervical carcinoma, breast cancer, lung carcinoma,[13] colon

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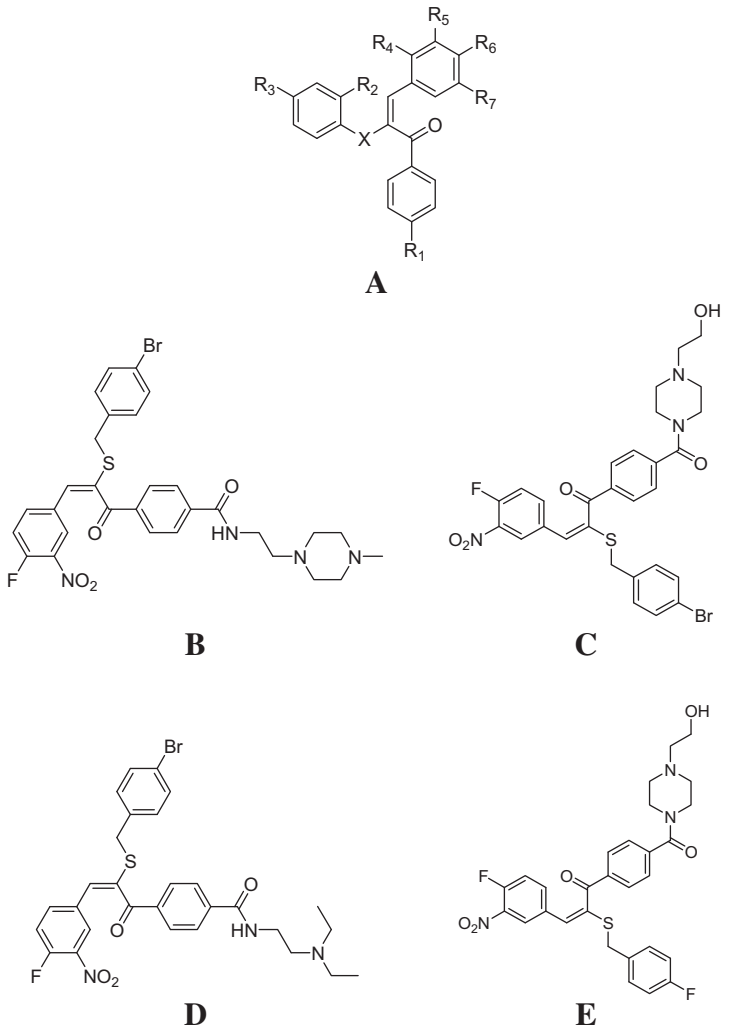

Figure 1 Basic structures of chalcone series.

cancer,[14,15] chronic myelogenous leukemia,[16] and prostate cancer.[17] *α-benzylthio chalcone was discovered as a new class of BCR–ABL tyrosine kinase inhibitors* that exhibit cytotoxicity against leukemia (K562) cells.[16]

3D-QSAR is a quantitative correlation between structure and experimental activity of the compounds.[18] 3D-QSAR model is developed by using three dimensional conformers of active compounds and score a compound on the basis of fitting function that evaluate the alignment of three dimensional chemical features (hydrogen donor, hydrogen acceptor, hydrophobic groups, chargeable group, and aromatic rings) of the model.[19] The activity of new compounds can be quantitatively predicted by evaluating how well each compound maps onto the pharmacophore model.[20]

In the present study, pharmacophore models have been generated and validated for the prediction of BCR–ABL tyrosine kinase inhibitory activity of α-benzylthio chalcone derivatives using the PHASE module of Schrodinger suite. The alignment obtained from the pharmacophoric points is used to derive a pharmacophore based 3D-QSAR model.[20]

2. Experimental

2.1. Dataset

A series of 33 α-benzylthio chalcone derivatives having BCR–ABL kinase inhibitory activity in leukemic K562 cells was used for the present studies.[16] The IC_{50} values of BCR–ABL kinase inhibitory activity were converted to pIC_{50}. Dataset was divided randomly into training and test set by considering the 50% of the total molecules in the training set (seventeen molecules) and 50% in the test set (sixteen molecules). Training set was used to generate pharmacophore models and the proposed models were validated by predicting the activity of test set molecules. The basic structure for chalcone derivatives is depicted in Fig. 1 and various substituents are enlisted in Table 1.

2.2. Pharmacophore modeling

In the present work, PHASE[21] software has been used to generate pharmacophore models. The structures of all the training set molecules were drawn using maestro[22] and then subjected