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QSAR STUDIES OF PYRAZOLE DERIVATIVES CONTAINING THIOUREA AS TYROSINE KINASE INHIBITORS

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ABSTRACT: A QSAR studies on pyrazole derivatives as specific anticancer agents was performed with 37 (32 training + 5 test) compounds. QSAR studies were performed using chemOffice 6.0 software supplied by Cambridge soft. The sketched structures were subjected to energy minimization and then used to calculate the physiochemical properties. The regression analysis was carried out using a computer program called VALSTAT. The best models were selected from the various statistically significant equations. The study revealed that descriptors molecular weight (MW) and Connolly solvent excluded volume (cn sev) reduces the activity, where as molar refractivity (MR) enhances the anticancer activity. The analysis resulted in QSAR equation, which suggests that, n=27, r = 0.9115, r^2 = 0.8308, adjusted r^2 = 0.8087, standard deviation (std) = 0.0915 and q^2 = 0.7644. The results obtained from QSAR studies could be used in designing better anticancer agents among the congeners in future.

INTRODUCTION: The investigation of the quantitative structure activity relationships (QSAR) of substances is an important aspect of modern chemistry, biochemistry, medicinal chemistry, and drug discovery. The information obtained is composed of mathematical equations relating the chemical structure of the compounds to a wide variety of their physical, chemical, biological and technological properties. Once a correlation between structure and activity/property is found, any number of compounds, including those not synthesized yet, can readily be screened for selection of structures with desired properties.

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Hence, it is possible to select the most promising compounds for synthesis and testing in the laboratory [1–5]. Cancer, the uncontrolled, rapid and pathological proliferation of abnormal cells, is the second leading cause of human death after cardiovascular diseases in developing as well as advanced countries [6]. Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Cancer causes about 13% of all deaths. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells.

These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer promoting genetic abnormalities may be randomly acquired through errors in DNA (Deoxyribonucleic acid) replication or are inherited, and thus present in all cells from birth.

Although there are many therapeutic strategies including chemotherapy and radiotherapy, high systemic toxicity and drug resistance limit the successful outcomes in most cases. Therefore, novel diagnosis, treatment and prevention approaches are urgently needed for cancer therapy [7-8]. Cancer chemotherapy has entered a new era of molecularly targeted therapeutics, which is highly selective and not associated with the serious toxicities of conventional cytotoxic drugs. Receptor protein tyrosine kinases play a key role in signal transduction pathways that regulate cell division and differentiation. Among the growth factor receptor kinases that have been identified as being important in cancer is epidermal growth factor receptor (EGFR) kinase. Activation of EGFR may be because of over expression, mutations resulting in constitutive activation, or autocrine expression of ligand.

The role of EGFR has been most thoroughly studied in breast cancer, where it is over expressed in 25–30% of cases and is correlated with a poor prognosis. EGFR over expression is also seen in ovarian cancer [9]. The thiourea and urea derivatives play important role in anticancer agents because of their good inhibitory activity against receptor tyrosine kinases (RTKs), protein tyrosine kinases (PTKs), and NADH oxidase, which play critical roles in many aspects of tumorigenesis. Many pyrazole derivatives are acknowledged to possess a wide range of bioactivities. The pyrazole motif makes up the core structure of numerous biologically active compounds. Thus, some representatives of this heterocycle exhibit anti-viral/anti-tumor [10]. Much attention was paid to pyrazole as a potential antimicrobial agent after the discovery of the natural pyrazole C-glycoside, pyrazofurin which demonstrated a broad spectrum of antimicrobial activity.

However, to our knowledge, few reports have been dedicated to the synthesis and EGFR inhibitory activity of pyrazole derivatives containing thiourea skeleton [11]. In the present study, we have performed the quantitative structure activity relationship analysis by various regression methods. Regression methods are used to build a QSAR model in the form of a mathematical equation. This equation explains variation of dependent in terms of independent variables. The QSAR model can be used to predict activities for new molecules, for screening a large set of molecules whose activities are not known.

MATERIAL AND METHODS: The data set of 37 molecules with their anticancer activity has been taken from the published results [11]. Anticancer activity was expressed as IC_{50} (µm) values which were converted into –log IC_{50} for convenience of computational work. It is essential to assess the predictive power of the models by using a test set of compounds. This was achieved by arbitrarily setting aside some compounds as a test set.

Molecular Structure Generation: All structure of pyrazole derivatives compounds were constructed using ChemOffice 2003 version 6.0 software supplied by Cambridge Software Company, USA. All 2D (2-Dimentional) structure is converted into 3D (3-Dimentional) structures in Chem 3D in ChemOffice 2003[12].

Energy Minimization: The resulting 3D structures were then subjected to an energy-minimization process by using the molecular mechanics (MM2) method was applied to search for lower energy conformations for each molecule. The energy minimized molecules were re-optimizing using molecular orbital package (MOPAC).

Descriptors Calculation: The energy minimize structures was used for calculating various physicochemical descriptors like thermodynamic, electronic, steric and topological. Thermodynamic parameters describe free energy change during drug receptor complex formation. Spatial parameters are the quantified steric features of drug molecules required for its complimentary fit with receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and receptor.

Statistical Analysis: All the data set (37 molecules) were divided into two sets. First one training set having 32 molecules for generation of QSAR models and second test set having 5 molecules for validation of generated QSAR models. VALSTAT software was used to generate QSAR models by multiple linear regression analysis. Cross validation was performed using leave-one-out method.

For multiple linear regression analysis biological activity (-logIC_{50}) values was used as dependent variables and calculated parameters (descriptors) used as independent variables. The inter-correlation between the parameters was less than 0.5 which show inter-pair correlations among the selected descriptors are very low. Acceptability of the regression model was judged by examining the different statistical parameters i.e. number of samples in regression (n), regression coefficient (r), squared regression coefficient (r^2), adjusted squared regression coefficient (r^2adj), F-test (Fischer's value) for statistical significance, standard deviation (std), cross-validated squared correlation coefficient (q^2), boot strapped squared correlation coefficient (bsr^2), friedman lack of fit measure (LOF), quality factor (QF), probable Error of correlation (PE), Kubinyi function (FIT), Akaike's Information Criterion (AIC) and correlation matrix to show mutual correlation among the parameters.

RESULTS AND DISCUSSION: Four statistically significant QSAR models have been developed by using multiple linear regression analysis.

Model 1: BA = [3.98569(± 1.12963)] +MW [-0.00830316(± 0.00136759)] + Cnas [-0.0122442 (± 0.00277385)] + MR [0.114403 (± 0.0160581)] n = 30, r = 0.8138, r^2 = 0.6623, r^2adj = 0.6234, variance = 0.0463, std =0.2151, QF = 3.7826, PE = 0.0411, F=16.9997, FIT=1.3396, LOF=2.0476, AIC=0.0553

Model 1 explains only 66.2% variance in the anticancer activity. It shows that descriptor molecular weight (MW) and connolly accessible area (Cnas) contribute negatively; whereas molar refractivity (MR) contribute positively towards anticancer activity.

Model 2: BA = [29.8216 (± 3.81837)] +Homo [2.76231 (± 0.431208)] +Nonvdw [3.69903e-006(± 1.42212e-006)] +Pmix [-8.30969e-005(± 3.39441e-005)]

n = 32, r = 0.7815, r^2 = 0.6107, r^2adj = 0.5690, variance = 0.1530, std =0.3911, QF = 1.9980, PE = 0.04589, F = 14.6409, FIT = 1.0713, LOF = 7.0177, AIC = 0.1967

Model 2 explains only 61.2% variance in the anticancer activity. It shows that descriptor highest occupied molecular orbital (HOMO) and non vander walls (Nonvdw) contribute positively, where as principal moment of inertia x (Pmix) contribute negatively towards anticancer activity. It is not a very good significant equation, therefore new model required for good explained variance.

Model 3: BA = [3.01177(± 0.673679)] +MW [-0.0065386(± 0.000958467)] +Cnsev [-0.0288932 (± 0.0049609)] +MR [0.126232(± 0.0144277)] n = 29, r = 0.8789, r^2 = 0.7724, r^2adj = 0.7450, variance = 0.0220, std = 0.1484, QF = 5.921, PE = 0.0282, F = 28.2729, FIT = 2.3170, LOF=0.9572, AIC=0.0253

Model 3 explains only 77.2% variance in the anticancer activity. It shows that descriptor molecular weight (MW) and Connolly solvent excluded volume (Cnsev) contribute negatively, where as molecular refractivity (MR) contribute negatively towards anticancer activity. It is not a very good significant equation, therefore new model required for good explained variance.

Model 4: BA = [3.87157(± 0.429843)] +MW [-0.0040636(± 0.000697125)] +Cnsev [-0.0243882(± 0.00313334)] +MR [0.0947197(± 0.010074)] n = 27, r = 0.9115, r^2 = 0.8309, r^2adj = 0.8087, variance = 0.0081, std=0.0901, QF =10.1107, PE = 0.0217, F = 37.6459, FIT = 3.3534, LOF=0.3407, AIC=0.0086

Model 4 explains 83.1% variance in the anticancer activity with low standard error shows the relative good fitness of the model. It shows that descriptor molecular weight (MW) and connolly solvent excluded volume (Cnsev) contribute negatively; whereas molar refractivity (MR) contribute positively towards anticancer activity. Molar refractivity (MR), a steric parameter, which is positively correlated, indicates that sterically bulky substituent would increases the binding affinity. The graph between experimental and predicted biological activity of training set compounds by using model 4 is shown in **Fig. 1.**

The validation criteria for selection of the model are cross validated squared correlation coefficient (q^2). The cross validation correlation coefficient (q^2) was 0.7644 means model 4 have good predictive power. The graph between experimental

BA and predicted BA of test set compounds by using model 4 is shown in **Fig. 2**.

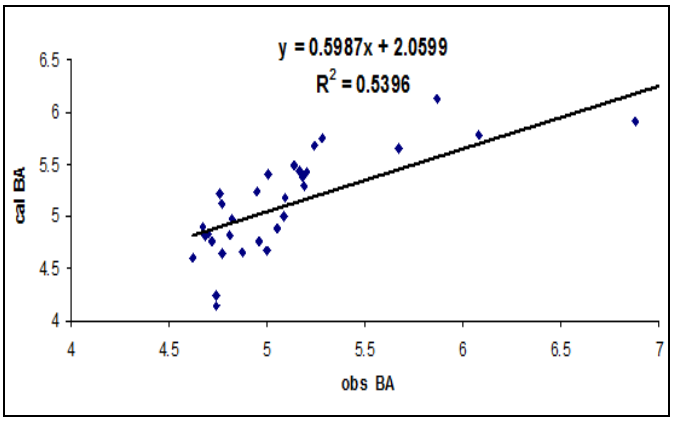

FIG 1: EXPERIMENTAL VS PREDICTED BIOLOGICAL ACTIVITY (BA) OF TRAINING SET COMPOUNDS BY MULTIPLE LINEAR REGRESSION MODEL.

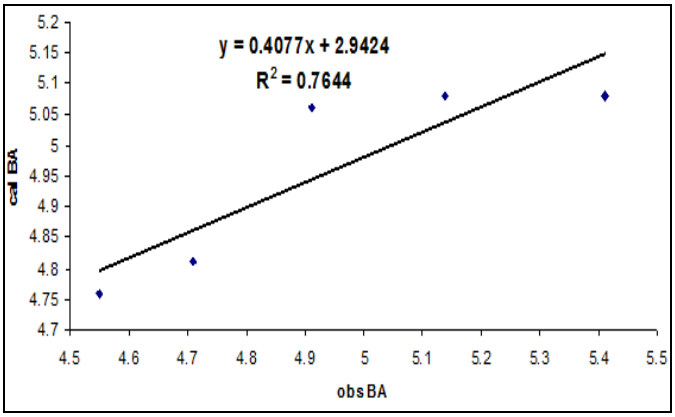

FIG. 2: EXPERIMENTAL VS PREDICTED BIOLOGICAL ACTIVITY (BA) OF TEST SET COMPOUNDS BY MULTIPLE LINEAR REGRESSION MODEL.

CONCLUSIONS: In summary, from the derived QSAR model it can be concluded that anticancer activity of pyrazole derivative containing thiourea is strongly influenced by the steric, electrostatic interactions and hydrophobic interaction nature of substituents. The model obtained by this study will used for designing of new compounds. Consequently this study may prove to be helpful in development and optimization of existing anticancer activity of this class of compounds.

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