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A two-dimensional quantitative structure-activity relationship investigation on 3-thiocyanato-1H-indoles as possible anticancer agents

V.Haribaskar, M.Gobinath , D.Ramesh & A.Ramesh

Abstract

We conducted two-dimensional quantitative structure activity relationship (2D QSAR) research on a new series of 3-thiocyanato-1H-indoles in an effort to identify powerful anti-cancer drugs. variety of 3-thiocyanato-1H-indoles were subjected to 2D-QSAR using Vlife MDS 4.3.The k-nearest neighbors (kNN) approach, used to Vlife molecular design suites (MDS), yielded a statistically verified two-dimensional quantitative structure activity relationship model. Cytotoxicity activity against the HL60 human cancer cell line was associated with Model 3 statistical data (q2 = 0.8001, pred r2 = 0.4082). The LOO approach was used for validation.Final Thoughts: The model now includes three attributes that positively correlate with the cytotoxicity activity. There is hope that novel, more effective anticancer drugs could be developed using this proven 2D QSAR model.

Keywords: 2-dimensional quantum search for anticancer drugs using regression analysis; 3-thiocyanato-1H-indoles; HL60 cell line.

Introduction

The unique capacity of the compounds produced by heterocyclic chemistry to bind reversibly to proteins and imitate the structure of peptides makes it a very useful source of new molecules with various biological functions.(1) to four (3) Indole, also known as benzopyrrole, is a heterocyclic compound with one nitrogen atom (N) substituted for one carbon atom in the ring. As a privileged structure that binds to several receptors with high affinity, the indole moiety is widespread and ranks among the most prevalent hetrocycles among physiologically active natural compounds, medicines, and agrochemicals (5). The therapeutic implications of Indole have been highlighted in published publications as follows: anti-viral, anti-depressant, anti-hyperlipidemic, anti-inflammatory, anti-psychotic, anti-microbial, anti-oxidants, anti-HIV, immunomodulator, anti-leukemia, (19).(21-22) Natural substances with strong pharmacodynamic Indole nucleus activity include reserpine, bufotenine, tryptophan, serotonin, vinblastine, vincristine, tryptamine derivatives, and others. As the second-biggest killer of humans, cancer poses a serious danger to human health.chapters 29–32) The World Health Organization (WHO) projects that 12 million people will lose their lives to cancer by the year 2030.(33) radiation and chemotherapy are two of the current cancer therapies, however the most remarkable pharmaceutical approach to cancer would still be a combination of radiation and significant surgery.

Department of Pharmacy
Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore Dt.524001 A.P. India

History of Medicine Studies
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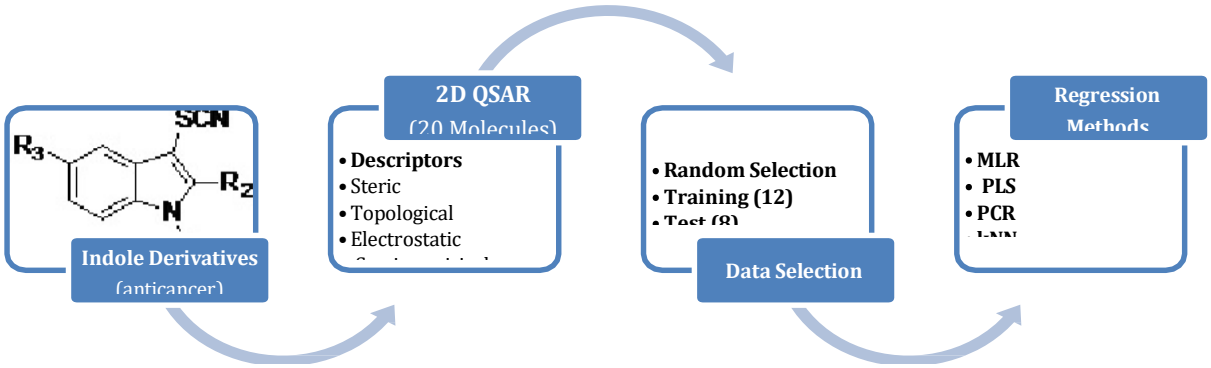
The limitations of the current anticancer drugs, including as their toxicity to normal cells and acquired tumor resistance, persist despite ongoing research. Thus, enhancing the pharmacological profile and conducting cutting-edge cancer research depend on the discovery of effective, safe, and selective anticancer agents.(34) For the purpose of predicting biological activities, especially in medication design, the quantitative structure-activity relationship (QSAR) method became very helpful and extensively used. The premise upon which this method rests is that alterations to their biological activity may be associated with changes to their chemical structures.places 35 and 36 Margiani et al. prepared a battery of 3-thiocyanato-1H-indoles and tested their cytotoxic effects on several cancer cell lines. Anticancer activities with improved treatment safety and effectiveness were the goals of this work, which intended to clarify the structural properties of 3-thiocyanato-1H-indole derivatives.(37)



Material and Methods

Computer aided drug designing based on quantitative structure activity relationship (QSAR) is the study of the quantitative relationship between the experimental activity of a set of compounds and their physicochemical properties. Different statistical approaches are used while building a QSAR model, where experimental information associated with biological activity, is used as dependent variable.[35-36] In the present study, all computational work (2D-QSAR) was performed using Vlife MDS 4.3 QSAR plus software on a HP Pentium IV 2.80 GHz Processor
/ Microsoft Win XP Home Edition system.

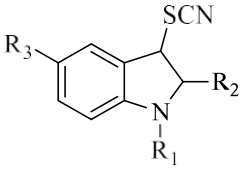
2D-QSAR modelling and dataset: Information on cytotoxicity-inducing activities Data from published sources were used to determine the IC50 (μM) of the twenty compounds listed in Table 1.(37) With the use of the Mosamann technique in an MTT test, the experimental IC50 values were determined for HL-60 cell lines; IC50 represents a 50% suppression of cancer development. Chemicals were deemed active if their pIC50 values were between 5.25 and 6.20. Table 2 lists the dependent variable for 2D investigations, which is the negative logarithm of the observed IC50 (μM) [pIC50 = -log (IC50)]. Chemdraw Ultra 8.0 was used to build 2D structures, which were then transformed into 3D ones using the same program. Molecular mechanics (MMFF) and Montocarlo conformational search were used to minimize energy and analyze conformations of all three-dimensional molecules until the RMS gradient value was less than 0.001 kcal/mol Å. In order to determine the physicochemical properties of stable molecules, this Montocarlo conformational search approach produces a number of different conformations after energy minimization. After initially calculating 240 2D descriptors using energy-minimizing geometry, the number was subsequently decreased to 156 using invariable column selection. The following steric, topological, electronic, molecular, and structural descriptors were computed: chiV6chain, chiV4pathcluster, Idw Average (steric), chi1, chi5, chiV0, chiV3, chiV4, chiV5, 3PathCount, chi6chain, chiV6chain, chiV3Cluster, 3ClusterCount, chi4pathCluster, chiV4pathCluster, 4pathClusterCount, kappa3, k1alpha, k2alpha, VChi 3 cluster, VChi 4 cluster, and VChi 5 path. The Kier symmetry index, the alpha 1 and alpha 3 shapes, and the Kier shape 2 Ch0, Ch2, and Chi 3

group, not Here are some terms related to Chi-square: VChi-1, VChi-3, VChi-4, VChi-4 path/cluster, Kier-1, Kier-3, Kier-alpha-2, Kier-flex, and Kier steric descriptor. Charge index 1, charge index 3, charge index 5, charge index 7, charge index 9, valence charge index 2, valence charge index 4, valence charge index 6, valence charge index 8, valence charge index 10, delta chi 0, delta chi 2, delta chi 3 cluster, delta chi 5 path, variation chi 1, variation chi

History of Medicine Studies
ISSN:1300-669
Volume 14 Issue 2 Aug 2018

3, variation chi 5, delta chi 1, delta chi 3 path, delta chi 4 path/cluster, variation chi 0, variation chi 2, bound charge index 2, k2alpha With a topological chi-five route and zero path count, Various terms such as maximum positive charge, maximum positive hydrogen charge, relative negative charge, hydrophobic SA-MPEOE, negative charged polar, maximum negative charge, charge polarization, polarity parameter, and relative positive charge are used. surface area with a positive potential, surface area with a negative potential, average potential, average +ve potential, average -ve potential, distance between the most positive and negative potential, average -ve potential (electronic), and so on.

Table 1: Series of 3-thiocyanato-1*H*-indole derivatives



Compound no.	R1	R2	R3
1	H	H	H
2	H	H	4-Me-C_6H_4
3	H	H	OMe
4	H	H	Br
5	H	H	CN
6	Ph	H	H
7	Me	H	4-Me-C_6H_4
8	4-MeO-C_6H_4	H	H
9	Me	H	H
10	4-Cl-C_6H_4	H	H
11	H	C_6H_5	H
12	H	4-Me-C_6H_4	H
13	H	4-MeO-C_6H_4	H
14	H	3CF_3-C_6H_4	H
15	H	4-Cl-C_6H_4	H
16	Me	C_6H_5	H
17	Me	4-Me-C_6H_4	H
18	Me	4-MeO-C_6H_4	H
19	Me	3CF_3-C_6H_4	H
20	Me	4-Cl-C_6H_4	H

Table 2: Observed and Predicted activities of compounds

Compound no.	Actual/Observed Activity	Predicted Activity
1	5.49	5.38
2	6.59	6.17
3	5.25	5.51
4	5.52	5.37
5	5.25	5.45
6	5.84	5.92
7	5.39	5.52
8	5.85	5.85
9	5.81	5.85
10	5.45	5.49
11	6.20	6.06
12	5.64	6.18

History of Medicine Studies
ISSN:1300-669
Volume 14 Issue 2 Aug 2018

13	5.35	6.08
14	6.16	6.18
15	5.97	5.84
16	5.86	5.86
17	5.82	5.89
19	5.59	5.42
20	5.96	5.85

Selection of training and test set: A data set of 20 molecules belonging to 3-thiocyanato-1*H*-indoles derivatives as anticancer agents were taken from the literature[37] and used for QSAR study. The dataset was divided into training set (12 compounds) and test set (8 compounds) by Sphere Exclusion (SE) method for principal component regression (PCR), multiple linear

regression (MLR), partial least squares (PLS), k-nearest neighbours (kNN) model. In classical sphere exclusion algorithm, each selected molecule generates a hyper- sphere around itself, where any molecule inside the sphere is excluded from the selection in the train set and driven towards the test set. The number of compounds selected and the diversity among them can be determined by adjusting the radius of the sphere (R). Inhibitory activity i.e. pIC_{50} has been considered as dependent variable and the remaining descriptors as independent parameters.

Regression analysis: Quantitative Structure-Activity Relationship (QSAR) analysis is a parametric method that researchers use to learn about the action mechanism and key structural components of a class of drugs. Specifically, 20 compounds were tested for their biological activity using regression analysis, PCR, MLR, PLS, and kNN as statistical methods. Correlative parameters were chosen based on their physicochemical or structural properties. Using a cross-correlation threshold of 0.7, four variables were included in the final equation for PCR, MLR, and PLS. The term selection criteria included r2, F-test 'in,' at 4, and 'out,' at 3.99, in addition to r2 and the F-test. We set the scaling to auto scaling, set the variance cut off to 0.1, and set the number of random iterations to 10. For the purpose of evaluating QSAR models, the following statistical measures were utilized: n, the number of chemicals in regression, r, the number of descriptors in a model, k, and the F-test (Fisher test value) for statistical significance. Equations (F), (q2), (pred_r2), (r2 se) and (q2 se) represent the standard error (SE) of estimate, as well as the cross-validated correlation coefficient and the predictive squared correlation coefficients. The relative fit of the regression equation is measured by the regression coefficient r2. For a better regression fit, the values of the correlation coefficient should be closer to1.0, the significance level. The ratio of the variation explained by the model to the variance owing to the error in the regression is shown in the F-test. A statistically significant model is one with a high F-test score. One of the validation parameters, predictive r2 (r2_pred), was computed to assess the model's predictive ability; a value higher than 0.5 indicates that the QSAR model has strong predictive capacity. The biological activity was associated with the physico-chemical descriptor values using a variety of statistical models that were created using PCR, MLR, PLS, and kNN based regression techniques combined with forward, forward backward, genetic algorithm, and simulated annealing method.

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Validation of QSAR model: Model validation is done to analyse the internal stability and predictive ability of the QSAR models. The best to evaluate quality of regression model is internal and external validation. Internal validation is carried out using leave one out (q^2,

LOO) method. For calculating q^2 each molecule in the training set was eliminated once from training set and the activity of eliminated molecule was predicted by using model developed by the remaining molecules. This q^2 described the internal stability of the model[39] and is expressed as shown in equation (Eq A.1)

$$q2 = 1 - \Sigma (Y\,\text{pred} - Y\,\text{act})\,2 / \Sigma (Y\,\text{act} - Y\,\text{mean}) \quad \textbf{(Eq A.1)}$$

Secondly, the predictive ability of the model i.e. external validation was confirmed by comparing the observed value of the test set molecules with predictive value of test molecules and is indicated by predicted r^2 as shown in equation (Eq A.2).

$$\text{pred\_}r\,2 = 1 - \Sigma (Y\,\text{pred(Test)} - Y\,\text{Test})\,2 / \Sigma (Y\,\text{Test} - Y\,\text{Tr aining}) \quad \textbf{(Eq A.2)}$$

Results

Selected molecular parameters computed for all the 20 molecules were used to develop QSAR equation by relating their corresponding inhibitory activities i.e. IC_{50} values. Aim was to establish a predictive model with a number of logical descriptors to get good generalization performance and which can be further utilized for the synthesis of 3-thiocyanato-

1*H*-indoles as anticancer agents. Various models were developed using, PCR, MLR, PLS and kNN and the model having best fit with minimum number of descriptors has considered or found to be the best model. When this point is achieved, no further considerable improvement in the regression coefficient (r^2 and q^2) values were observed even if a new descriptor is added. In the present study PCR, MLR, PLS and kNN, methods employing three, four or more variable combinations for combined dataset generated around 300, equations out of which, the reasonable acceptable ones were selected for discussion. The different models generated for better correlation by statistical analysis have been given in **Table 3**, whereas **Table 4** contains various descriptors, their categories as well as their contribution towards each descriptor.

Table 3: Various significant models obtained by MLR and kNN methods and their statistical parameters

Model	Equation	N	r^2	q^2	Pred r^2	F-test
MLR (SA)	Eq B.1	14	0.9393	0.6493	0.3052	4.6419
kNN (SA)	Eq C.1	15	-	0.7224	0.3867	-
kNN (SA)	Eq D.1	16	-	0.8001	0.4082	-

Table 4: Various descriptors obtained by MLR method (Eq B.1); their categories, contributions and significance

Descriptor	Category	Contribution	Significance
Average –ve Potential	Electrostatic	+	total -ve electrostatic potential on van der Waals surface area of the molecule
Bromione Count	Element count	+	number of bromine atoms in a compound
SsCH3Count	Estate Numbers	-	total number of –CH3 group connected with single bond
Idw Average	Information Theory Based	+	information-based descriptors
SA Hydrophilic Area	Hydrophobicity	-	vd W surface descriptor showing hydrophobic surface area
-Ve Potential Surface Area	Electrostatic	-	total van der Waals surface area with negative electrostatic potential of the molecule
SK Most Hydrphobic Hydrophilic Distance	Hydrophobicity	-	total van der Waals surface area with negative electrostatic potential of the molecule
SA Most Hydrphobic Hydrophlic Distance	Hydrophobicity	+	distance between most hydrophobic and hydrophilic point on the vdW surface
XK Most Hydrophobic Hydrophilic Distance	Hydrophobicity	+	distance between most hydrophobic and hydrophilic point on the vdW surface
+ve Potential Surface Area	Electrostatic	+	total van der Waals surface area with positive electrostatic potential of the molecule

Eq B.1 represents the model 1, obtained by MLR regression analysis

$$pIC_{50} = +13.9818\ (\text{Average–ve Potential}) +0.0709\ (\text{Bromione Count}) -0.1108\ (\text{SsCH3Count})$$

History of Medicine Studies
ISSN:1300-669
Volume 14 Issue 2 Aug 2018

+1.5159 (Idw Average) -0.0574 (SA Hydrophilic Area)
-0.0163 (-ve Potential Surface Area)
-0.0277 (SK Most Hydrphobic Hydrophilic Distance)
+0.0842 (SA Most Hydrphobic Hydrophlic Distance)
+0.1995 (XK Most Hydrophobic Hydrophilic Distance)
+0.0200(+ve Potential Surface Area) (**Eq B.1**)

Contributions of the various descriptors, fitness plots and actual and predicted of the training and sets molecules w.r.t. MLR model are shown in **Fig. 1, 2**. Model with low pred r^2 0.3052 (31%), and cross-validated correlation coefficient q^2 0.6493 was not found to be satisfactory for a good correlation between the structure and activity.

k-Nearest Neighbour method using simulated annealing (SA) was performed in order to get improved QSAR models, kNN imethod is used for modelling linear relationship between a dependent variable *Y* (pEC_{50}) and independent variable *X* (2D descriptors). In this method, an unknown pattern is classified according to the majority of the class membership of its k nearest neighbors in the training set. The nearness is measured by an appropriate distance metric (e.g. a molecular similarity measure, calculated using field interactions of molecular structures).[40] Using same data set, a new kNN based model 2 (Eq C.1) was generated.

pIC_{50}= 0.0809 0.0845(SaasN(N oxide)count) +1.0000 1.0000 (XK Hydrophobic Area) + 362.3820 366.7580 (SssO count) (**Eq C.1**)

Generated QSAR model 2 (kNN method) shows high cross-validation correlation coefficient, *q2* between descriptors (SaasN(N oxide)count, XK Hydrophobic Area, SssO count) and cytotoxicity activity, but the low r^2 value 0.3867 i.e. predicted correlation coefficient, indicates the model is not significant. **Fig. 3** shows the fitness plot and actual & predicted activity of the training and test molecules.

The compound 18 was found to be an outlier and its omission resulted into model 3 with improved correlation i.e. **Eq. D.1** and was found to be the best model that exhibits good external pre-dictivity indicated by pred r^2 0.4082 and cross-validated correlation coefficient q^2 0.8001 using kNN by simultated annealing method. The fitness plot and of observed, predicted activities of the 20 molecules have been given in **Fig. 4.**

pIC_{50}= 0.0000 0.0000 (H-Donor Count) + 360.7880 361.3780 (SA Hydrophobic Area) + 9.2460 9.2570 (StNE-index) **(Eq D.1)**

The best model is indicating the effect of H-Donor Count, SA Hydrophobic Area and StNE-index on the biological activity. H-Donor Count an individual descriptor defines the number of hydrogen bond donor, but in the present studies no significant correlation has been found with biological activity as indicating in the equation with its value ranging from 0.0000 0.0000. SA Hydrophobic Area descriptor is a hydrophobic Slog P descriptor describing the hydrophobic surface area, and present equation has indicated its positive correlation (360.7880 361.3780) with the biological activity. It means higher the hydrophobic surface area higher would be the anticancer activity. The importance of number of nitrogen atom connected with one triple bond is further indicated by StNE-index descriptor, an estate contribution descriptor. Descriptor has been found to be positive correlated with the biological activity with value ranging from 9.2460 - 9.2570 thus greater contribution of StNE-index results into greater cytotoxicity against cancer cell line HL60.

Table 5: Various descriptors obtained by kNN (Eq C.1) method; their categories, contributions and significance

Descriptor	Category	Contribution	Significance
SaasN(N oxide)count	Estate Numbers	+	total number of nitro oxide group connected with one single along with two aromatic bonds
K Hydrophobic Area	Hydrophobicity X log pK	+	total number of oxygen connected with two single bonds
SssO count	Estate Number	+	total number of oxygen connected with two single bonds

Table 6: Various descriptors obtained by kNN (Eq D.1) method; their categories, contributions and significance

Descriptor	Category	Contribution	Significance
H-Donor Count	Individual	+	number of hydrogen bond donor atoms
SA Hydrophobic Area	Hydrophobicity Slog pA	+	descriptor showing hydrophobic surface area
StNE-index	Estate contributions	+	number of nitrogen atom connected with one triple bonds

Conclusions

To test their potential anticancer effects, 20 compounds of 3-thiocyanato-1H-indoles were run through a 2D-QSAR. Results from the current series of 3-thiocyanato-1H-indoles shown high correlation, as shown by the best model 3 with q2 = 0.8001 and pred r2 = 0.4082 as anticancer activity against cell line (HL-60). All of the suggested QSAR models were statistically significant. The QSAR model's predictive capabilities were examined using the LOO approach, which yields impressive internal predictivity. Numerous physicochemical characteristics were shown to have an effect on the cell line (HL-60) in the QSAR investigation. These included the SA Hydrophobic Area (which had a positive contribution), the StNE-index (which had a positive contribution), and H-Donor Count (which had no effect). These findings will be useful in the development of novel anticancer drugs derived from 3-thiocyanato-1H-indoles.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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