 DOI: 10.18231/2394-2797.2016.0003

3-Thiocyanato- 1*H*- indoles as potential anticancer agents: Two dimensional quantitative structure activity relationship study

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Abstract

Introduction: In an attempt to find potent anti-cancer agents, we performed two-dimensional quantitative structure activity relationship (2D QSAR) studies, on a novel series of 3-thiocyanato-1H- indoles.

Method: 2D-QSAR was performed using Vlife MDS 4.3 on a series of 3-thiocyanato-1*H*-indoles.

Result: The statistically validated two-dimensional quantitative structure activity relationship model was obtained through k-nearest neighbors (kNN) method using Vlife molecular design suits (MDS). Statistical data of Model 3 (q^2 = 0.8001, pred r^2 = 0.4082) correlated with cytotoxicity activity against human cancer cell line (HL60). Validation was done with LOO method.

Conclusion: Three descriptors showing positive correlation with the cytotoxicity activity have been included in the model. This validated 2D QSAR model may be used to new more potent anticancer compounds.

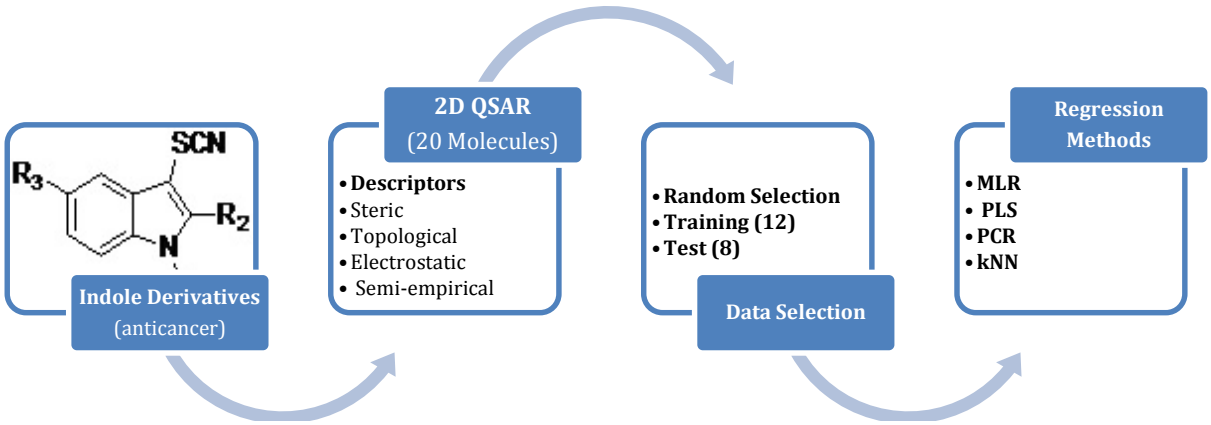
Keywords: 2D-QSAR; anticancer agents, regression analysis; 3- thiocyanato-1*H*-indoles; HL60 cell line.

Introduction

Heterocyclic chemistry is one of the most valuable sources of novel compounds with diverse biological activities, because of the unique ability of the resulting compounds to mimic the structure of peptides and to bind reversibly to proteins.[1–4] Indole (benzopyrrole) is an heterocyclic structure in which one carbon atom of the ring has been replaced by hetero atom nitrogen (N). Indole moiety has been described as the most abundant hetrocycles among biologically active natural products, pharmaceuticals, agrochemicals[5] and known as ubiquitous and privilaged structure,[6,7] that bounds to the multiple receptors with high affinity. Published reports on Indole has indicated their therapeutic implications as anti-viral,[8-10] anti-depressants,[11] anti-hyperlipidemic,[12] anti-inflamatory,[13-14] anti-psychotic,[15] anti-microbial,[16-17] anti-oxidants,[18] anti-HIV,[19] immunomodulator[20] and anti-leukamia.[21-22] On the other hand natural products like reserpine,[23] bufotenine,[24] tryptophan,[25] serotonin,[26] vinblastine, vincristine,[27] tryptamine derivatives[28] have been found to posses potent pharmacodynamic Indole nucleus.

Cancer represents one of the biggest threats to human health and is the second leading cause of human mortality.[29-32] According to World Health Organization (WHO) statistics, it is estimated that there will be 12 million deaths from cancer upto 2030.[33] Current treatments for cancer involve chemotherapy, radiotherapy, but extensive surgery with chemotherapy would remain the most noteworthy pharmacological approximation to cancer. Despite continued research efforts, the existing anticancer agents suffers from limitations like toxicity to normal cells and acquired tumor resistance. Therefore, the search for potent, safe and selective anticancer compounds is a crucial aspect of modern cancer research and to improve pharmacological profile.[34]

The quantitative structure-activity relationship (QSAR) approach became very useful and largely widespread for the prediction of biological activities, particularly in drug design. This approach is based on the assumption that the variations in the chemical structure can be correlated with changes in their biological activities.[35-36] Margiani *et. al*, have synthesized a series of 3-thiocyanato-1*H*-indoles and evaluated these Indoles for their cytotoxic activity against different cancer cell lines. This study aimed to elucidate the structural features of 3-thiocyanato-1*H*-indole derivatives required for anticancer activities with greater therapeutic safety and efficacy.[37]

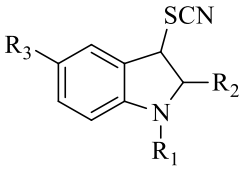


Material and Methods

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: Cytotoxicity-inducing activity data IC_{50} (μM) of the twenty molecules **Table 1** were taken from the published data.[37] The experimental IC_{50} values were evaluated by Mosamann method in a MTT assay,[38] using cell lines (HL-60), and IC_{50} representing 50% inhibition of the cancer growth. Compounds having pIC_{50} ranging from 5.25 to 6.20 has been considered as active. The negative logarithm of the measured IC_{50} (μM) [pIC_{50} = -log (IC_{50})] was used as dependent variable for 2D studies and it is listed in **Table 2**. Two-dimensional (2D) structures were constructed using Chemdraw Ultra 8.0, and then converted to three-dimensional (3D) structures in same software. All 3D molecules were subjected to energy minimization using molecular mechanics (MMFF) and conformational analysis using Montocarlo conformational search until the root mean square (RMS) gradient value reaches a value smaller than 0.001 kcal/mol Å. This Montocarlo conformational search method generates various conformations of the stable molecules after energy minimization and calculates its physicochemical descriptors. Energy-minimized geometry was used for calculation of descriptors, a total of 240 2D descriptors were calculated, eventually reduced to 156 after applying invariable column selection. The steric, topological, electronic, thermodynamic, molecular, and structural descriptors calculated were consists of 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, VChi 5 path, Kier shape 2, Kier alpha 1, Kier alpha 3, Kier symmetry index, Chi 0, Chi 2, Chi 3 cluster, Chi 5 path, VChi 1, VChi 3 path, VChi 4 path, VChi 4 path/ cluster, Kier shape 1, Kier shape 3, Kier alpha 2, Kier flexibility, Kier steric descriptor, Delta Chi 0, Delta Chi 2, Delta Chi 3 cluster, Delta Chi 5 path, difference chi 1, difference chi 3, difference chi 5, Delta Chi 1, Delta Chi 3 path, Delta Chi 4 path, Delta Chi 4 path/cluster, difference chi 0, difference chi 2, 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, bound charge index 2, k2alpha, Chi 5 path, 0PathCount, (topological), Max. positive charge, max. positive hydrogen charge, local dipole index, relative negative charge, hydrophobic SA–MPEOE, negative charged polar, max negative charge, total positive charge, charge polarization, polarity parameter, relative positive charge, +ve potential surface area, -ve potential surface area, most +ve potential, most -ve potential, average potential, average +ve potential, average -ve potential, most +ve & -ve potential distance, average potential, average +ve potential, average -ve potential (electronic).

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
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: QSAR is a parametric approach applied to set of series of compounds in order to understand their mechanism of action and important contributory structural factors responsible for activity. In this regard selected physicochemical or structural parameters were used as the correlative parameters and related to the observed biological activity of the 20 molecules by regression analysis PCR, MLR, PLS and kNN as statistical approaches. The cross-correlation limit was set at 0.7, number of variables in the final equation obtained were four in all PCR, MLR and PLS and term selection criteria as r^2, *F*-test 'in,' at 4 and 'out' at 3.99, r^2, and *F*-test. Variance cut off was set at 0.1, scaling to auto scaling, and number of random iterations to 10. Statistical measures were used for the evaluation of QSAR models were the number of compounds in regression *n*, multiple correlation coefficient (r), coefficient of determination (r^2), number of descriptors in a model *k*, *F*-test (Fisher test value) for statistical significance *F*, cross-validated correlation coefficient q^2, predictive squared correlation coefficients pred_r^2, coefficient of correlation of predicted data set pred_r^2*se* and standard error (SE) of estimation r^2 *se* and q^2 *se*. The regression coefficient r^2 is a relative measure of fit by the regression equation. The correlation coefficient values must be closer to 1.0 that represents the better fit of the regression. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. Predictive r^2 (r^2_pred) is the one of the validation parameter, that was calculated for evaluating the predictive capacity of the model and if its value greater than 0.5, means of the QSAR model has good predictive capacity. The number of statistical models were developed using PCR, MLR, PLS and kNN based regression methods coupled with forward, forward backward, genetic algorithm and simulated annealing method and correlated the biological activity with the physico-chemical descriptor values.

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)

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

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).

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

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 (Average–ve Potential) +0.0709 (Bromione Count) -0.1108 (SsCH3Count)
+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

A set of 20 molecules of 3-thiocyanato-1*H*-indoles were subjected to 2D-QSAR analysis for anticancer activity. All the proposed QSAR models were statistically significant, but results obtained for the present series of 3-thiocyanato-1*H*-indoles showed good correlation as manifested from the best model 3 with $q^2 = 0.8001$ and pred $r^2 = 0.4082$ as anticancer activity against cell line (HL-60). The prediction power of the QSAR model was tested by LOO method, which gives a good internal predictivity. QSAR study indicated the influence of various physicochemical parameters, including H-Donor Count (zero contribution), SA Hydrophobic Area (positive contribution), StNE-index (positive contribution) and many other descriptors used against cell line (HL-60). These results will be helpful in designing new 3-thiocyanato-1*H*-indoles derivatives as potential anticancer agents.

Conflict of interest

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

Acknowledgment

The authors are thankful to the Dr Amit Bedi, and Dr Kundan; Vlife Science Technologies Pvt. Ltd, Pune, India, for providing us with the Vlife MDS 4.3 software and for their continual support in the QSAR study. The grants received from Department of Science and Technology (DST), are gratefully acknowledged.

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