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Quantitative Structure Activity Relationship Study of Naphthoquinone Analogs as Possible DNA Topoisomerase Inhibitors

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ABSTRACT

Quantitative Structure Activity Relationship (QSAR) is among the most widely used computational technology for analogue-based drug design. A molecular modeling approach of Naphthoquinone (NQ) analogue as anticancer activity from recently reported literature were taken and was QSAR model was generated by using MOE 2009.10. DNA topoisomerases are enzymes that alter DNA topology by causing and resealing DNA strand breaks. The quinone nuclei, which can inhibit the activity of topoisomerase. In order to develop a new pharmacophoric model for this inhibition, a QSAR approach of reported NQ derivatives against cancer cell has been studied. Multiple linear regression analysis was performed to derive the quantitative structure activity relationship models which were further evaluated internally as well as externally for the prediction of activity. Accurate IC₅₀ values (μM) were collected for 26 analogs, and other descriptor parameters, such as log p (o/w), MR, DM, EELE, LUMO, HOMO, and TPSA were compared with these compounds. A training set of 26 analogs, all having a common NQ moiety, provided a cross-validated correlation coefficient (r²) value of 0.10835 and root mean square error value of 0.3951. The resulting QSAR pharmacophore model generated from the present study should be useful in the design of more potent substituted compounds of NQ targets as anticancer agents. Moreover, based on this QSAR study we have developed the 20 newly designed NQ derivatives and estimated their predicted IC₅₀ values theoretically by using trainpred.fit file which is generated by QSAR study of the training set compounds.

Keywords: QSAR, Naphthoquinone derivatives, Molecular descriptors, Topoisomerase inhibitors.

INTRODUCTION

Cancer is the second most common cause of death worldwide. Carcinogenic lacerations have been associated with deficient DNA repair. DNA topoisomerases are enzymes that alter DNA topology by causing and resealing DNA strand breaks. Tumors with high cell proliferation articulate these enzymes more than in normal cells, making topoisomerases good targets for the discovery of novel anticancer drugs [1]. The two types of DNA topoisomerases, i.e. Type I DNA topoisomerases (Topo I) break and rejoin only one of the two strands during catalysis, while Type II topoisomerases (Topo II) catalyze DNA topological changes by breaking both strands of the double helix and transporting another double-stranded DNA segment through the break and then re annealing the break [2]. On the other hand Topo II play an important role in DNA transaction *in vivo*, including chromosome condensation and segregation, and the removal of the super coils generated during replication and transcription [3] Studies in eukaryotes have shown Topo I to be associated with actively transcribed genes [4,5] whereas, Topo II is required for DNA replication and for successful traverse of mitosis [6-9].

Based on overall survival rates of cancer patients, which make us to vital search for new therapeutic agents to control cancer hopefully, which can be achieved by the development of novel compounds with promising anticancer activity. The numerous natural or synthetic substances containing the quinone nuclei, which is one of well-known nuclei can inhibit the activity of topoisomerase. The cytotoxic activity shown by this nuclei is mainly due to inhibition of DNA Topo II, through DNA alkylation or intercalation thereby, inhibiting the heat shock protein HSP90 and as well as through the formation of semiquinones and superoxide radicals, which contribute to the production of hydroxyl radical, the main source of oxidative generated damage to cellular DNA [10-12].

It has been established that many of the biological effects of quinone derivatives Such as the antitumor, antiproliferative, antibacterial, anti-inflammatory, antimalarial, antiviral, antifungal and antileishmanial effects depend on their 1,4-NQ pharmacophore group. NQs are molecules widely distributed in nature that possess a broad spectrum of biological activities and especially those containing nitrogen, have promising potential for the treatment of different diseases, including antibacterial, antifungal, antiviral, antiparasitic effects and anticancer activity [13,14].

Moreover, the incorporation of nitrogen and sulfur atoms on C2 and C3 of the 1,4-NQ lead could produce the compounds with diverse biological activities, including anticancer activity [15]. 1,4-NQ derivatives with an amino group at the 2-position have been reported to have good anti-neoplastic, [16,17] carcinostatic actions [18] and bacterial growth inhibition [19].

The increasing global cancer burdens its health and socio-economic impacts, the presence of drug resistance, etc. leads to the search for newer therapeutic agents with divergent and unique structure and with a mechanism of action possibly different from that of existing drugs are urgently required to tackle the menace. Therefore, the aim of this study is related to look for a newer analogue for the treatment of cancer with the help of Quantitative Structure Activity Relationship (QSAR) study on previously reported work [20]. This study suggests that, to build a QSAR model using multiple regression methods for NQ derivatives to explore the substitution requirement which is essential for the improvement of anticancer activity.

QSAR research has been considered a major tool in drug discovery to explore the ligand-receptor/enzyme interactions, especially when the structural details of the target are not known. QSAR can aid in identifying functional groups with their various structural parameters used to increase the bioactivity leads designing new structures with the variation in enhanced bioactivity depends on changes in chemical structure [21]. QSAR is an effective way for optimizing or correlating the biological activity within a congeneric sequence with certain structural parameters or with functional determinants, such as lipophilicity, polarizability, or electronic and steric properties [22]. Once a correlation between structure and activity/property is found, any number of compounds including those not synthesized, yet can readily be screened for the selection of structures with desired properties [23].

Moreover, in this proposed quantitative model, we tried to interpret the activity of these compounds based on the different multivariate statistical analysis methods like, the principal components analysis (PCA) and contingency analysis (CA), which is served to classify the compounds according to their activities and the variability of the descriptors. It allows reducing the number of variables not significant and making the information less redundant. The multiple linear regressions have served to select the descriptors used as the input parameters for the multiples non-linear regression and cross-validation to validate models used with the process leave-one-out (LOO). This study has an urge to put new efforts for finding new anticancer candidates with novel modes of action and to develop pipelines for drug discovery and development.

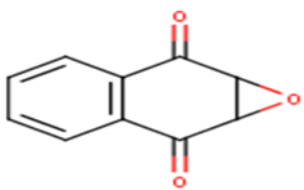
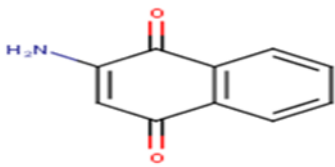
MATERIALS AND METHODS

IC₅₀ is defined as the concentration of an inhibitor where the response (or binding) is reduced by half. IC₅₀ values were manually converted into pIC₅₀ (predicted IC₅₀) using the formula of $pIC_{50} = -\log IC_{50}$. For the development of QSAR models of NQ analogues, a total number of 26 compounds selected from previously reported literature [20] and have been processed by using the software MOE 2009.10. Biological activity was selected as the dependent variable and around 7 molecular descriptors were selected as independent variables. The dataset molecules are validated by both internal and external validation procedures.

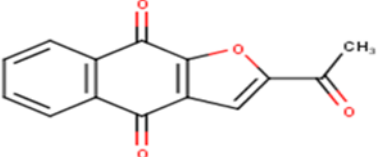
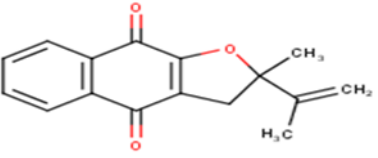
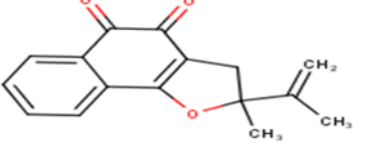
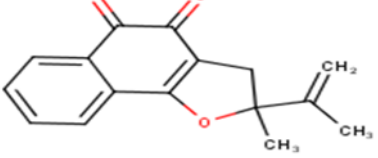
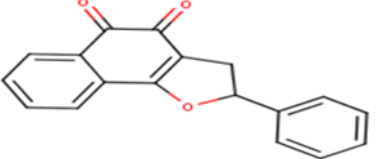
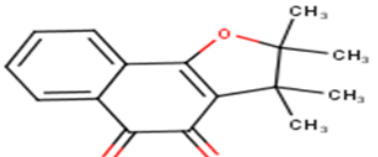
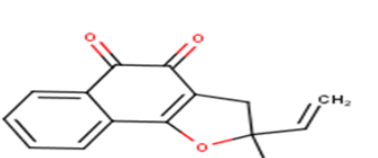
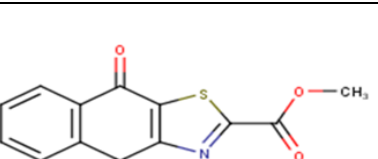
Dataset

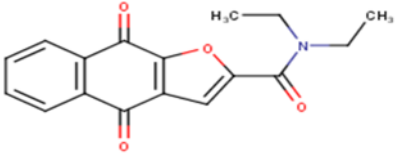
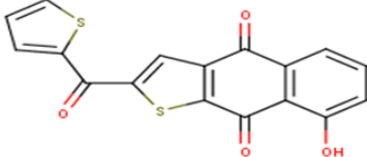
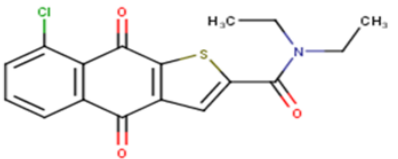
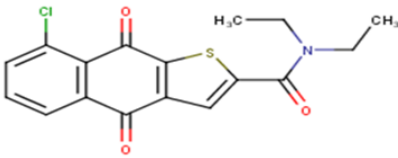
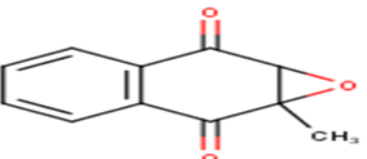
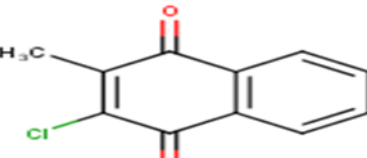
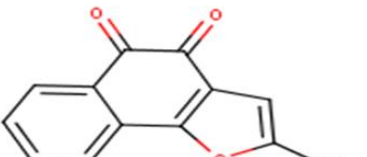
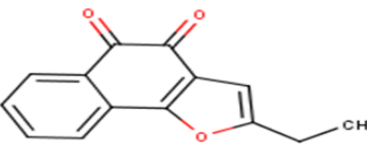
Thus, in this study we have selected a series of 26 NQ derivatives as training set which was previously synthesized by Julio et al., and they have investigated for their anticancer activity against HT-29 cells. Moreover, their results suggest that the toxicity is improved in molecules with tricyclic naphtho[2,3-b]furan-4,9-dione and naphtho[2,3-b]thiophene-4,9-dione systems 2-substituted with an electron-withdrawing group hence provide the hopeful hits for further anticancer drug development [20]. So, an attempt was made to establish a quantitative structure-activity relationship between anticancer activities with the series of 26 bioactive molecules derived from NQ moieties were performed by using multiple linear regression analysis. The structures of the training set of 26 NQ analogues were represented in Table 1. The micromolar concentration of IC₅₀ (μM) values was first converted into logarithmic values for performing the QSAR study. The Biological data used in this study were IC₅₀ values of NQ derivatives which are having an anticancer activity (Table 1).

Table 1: Molecular structure with observed and predicted activity of naphthoquinone derivatives used in training set

Code	Structure	IC ₅₀ (μM)	pIC ₅₀ (μM)		
			Observed	Predicted	Residual
1		10.76	4.9682	4.5907	0.3775
2		24.6	4.6091	4.5819	0.0272

3		40.18	4.396	4.7463	-0.3503
4		68.71	4.163	4.8636	-0.7006
5		17.62	4.754	4.7019	0.0521
6		24.95	4.6029	4.7509	-0.148
7		21.68	4.6639	4.8557	-0.1918
8		9.16	5.0381	4.8602	0.1779
9		8.2	5.0862	4.6545	0.4317
10		34.85	4.4578	4.95	-0.4922

11		4.61	5.3363	4.7915	0.5448
12		25.79	4.5885	4.8725	-0.284
13		28.08	4.5516	4.8752	-0.3236
14		30.25	4.5193	4.9198	-0.4005
15		14.76	4.8309	4.9226	-0.0917
16		18.11	4.7421	4.9093	-0.1672
17		88.1	4.055	4.8148	-0.7598
18		13.9	4.857	4.8406	0.0164

19		2.67	5.5735	5.0267	0.5468
20		1.73	5.762	5.0129	0.7491
21		6.89	5.1618	5.0787	0.0831
22		3.07	5.5129	5.0252	0.4877
23		4.242	4.242	4.6408	-0.3988
24		4.957 8	4.9578	4.631	0.3268
25		5.077 8	5.0778	4.7026	0.3752
26		4.863 9	4.8639	4.7519	0.112

Molecular descriptors

In this QSAR study, an about 7 descriptors were chosen to describe the structure of the compounds comprising the series to study viz. partition coefficients, molar refractivity, dipole moment, electrostatic interactions, lowest unoccupied molecular orbital (LUMO), highest unoccupied molecular orbital (HOMO), and topological polar surface area.

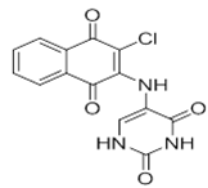
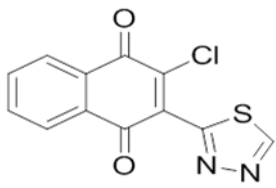
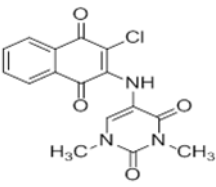
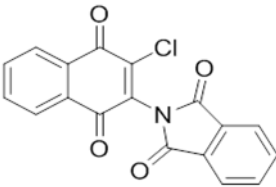
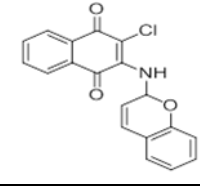
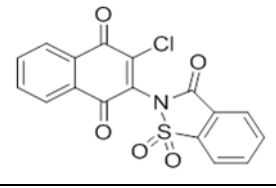
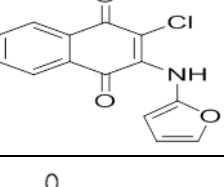
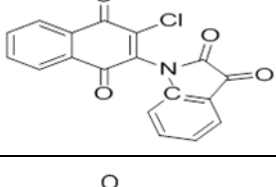
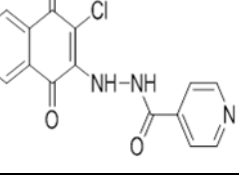
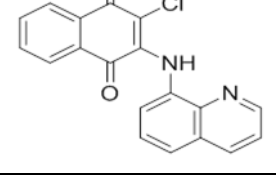
QSAR study

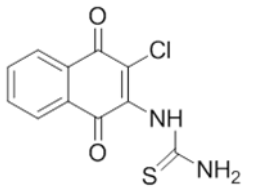
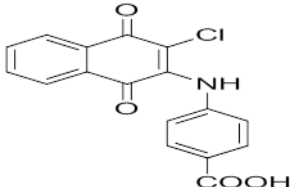
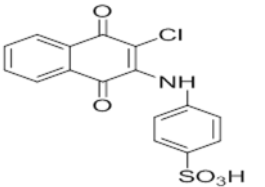
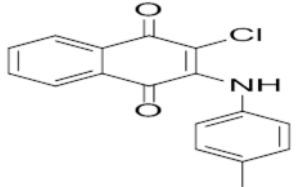
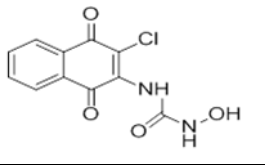
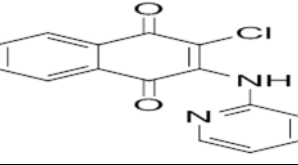
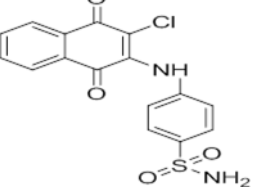
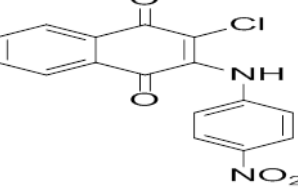
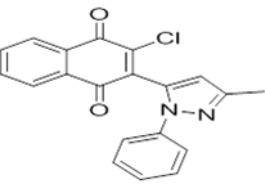
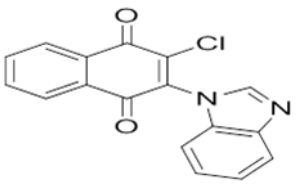
QSAR is an application of combinatorial chemistry to analyze experimental data and to build numerical models of the data for the prediction and interpretation. QSAR analysis was performed for 26 NQ compounds with their biological activity related to cancer, which was collected from the earlier reported literature [20] and the analysis was done by using the QSAR module on the software MOE 2009.10 [24]. The QSAR model was constructed for the above compounds with 7 selected molecular descriptors from the QSAR descriptor panel. The experimentally measured pIC_{50} (μM) for the 26 compounds of NQ derivatives against HT-29 cells were entered manually in the activity fields. The regression analysis was performed; the RMSE and R^2 values were derived from the QSAR fit. $\$PRED$ descriptor is the dependent variable for the activity field pIC_{50} generated by QSAR validate. A QSAR correlation plot was generated by plotting the values of pIC_{50} on the x-axis and the predicted values ($\$PRED$) on the y-axis for all the above 26 compounds. Furthermore, in order to identify the active compounds in the training set QSAR Contingency application was implemented and followed by principal component analysis (PCA) were performed and accordingly plotting a 3D graphical scatter plot with three vector values [25].

Design of new naphthoquinone derivatives

Based on the above QSAR model interpretation results in the identification of key structural features for improving the potency of the NQ molecules, which is used as a reference for building the newest NQ pharmacophore series. Therefore, the libraries of new structures containing the 20 compounds have been developed based on these QSAR results of NQ molecules (Table 2). Therefore, in this study, we investigated the newly designed 20 compounds of NQ derivatives containing nitrogen, oxygen and sulfur atoms, for their prediction as potential anticancer activity by the help of in-silico biological assays done on the QSAR study.

Table 2: Designed naphthoquinone derivatives for QSAR study

Compound	Structure	IUPAC name	Compound	Structure	IUPAC name
L1		5-((3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)pyrimidine-2,4(1H,3H)-dione	L11		2-chloro-3-(1,3,4-thiadiazol-2-yl)naphthalene-1,4-dione
L2		5-((3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione	L12		2-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)isoindoline-1,3-dione
L3		2-((2H-chromen-2-yl)amino)-3-chloronaphthalene-1,4-dione	L13		2-chloro-3-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)naphthalene-1,4-dione
L4		2-chloro-3-(furan-2-ylamino)naphthalene-1,4-dione	L14		1-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)indoline-2,3-dione
L5		N'-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)isonicotinohydrazide	L15		2-chloro-3-(quinolin-8-ylamino)naphthalene-1,4-dione

L6		1-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)thiourea	L16		4-((3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid
L7		4-((3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzenesulfonic acid	L17		2-chloro-3-(p-tolylamino)naphthalene-1,4-dione
L8		1-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-hydroxyurea	L18		2-chloro-3-(pyridin-2-ylamino)naphthalene-1,4-dione
L9		4-((3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzenesulfonamide	L19		2-chloro-3-((4-nitrophenyl)amino)naphthalene-1,4-dione
L10		2-chloro-3-((3-methyl-1-phenyl-1H-pyrazol-5-yl)amino)naphthalene-1,4-dione	L20		2-(1H-benzo[d]imidazol-1-yl)-3-chloronaphthalene-1,4-dione

RESULT AND DISCUSSION

In this study, training sets of 26 compounds were subjected to linear free energy regression analysis for model generation. Preliminary analysis was carried out in terms of correlation analysis. The correlations coefficients of different molecular descriptors with anticancer activity are presented in Table 3. Some statistically significant QSAR models were chosen for discussion. The derived models in QSAR from multiple linear regression shows good correlation between biological activity and parameters. The descriptors showed the positive correlation among all parameters selected for the QSAR model. The positive coefficients suggest that inclusion of such nitrogen, sulphur and oxygen atoms in the molecules lead to increase the biological activity. The computed molecular descriptors reported and predicted biological activities (pIC_{50}) of the ligand training set were shown in Table 1.

In order to validate the anticancer activity, the QSAR model was constructed for these 26 compounds with experimentally derived pIC_{50} (μM) values, system predicted pIC_{50} , \$PRED, and all other standard molecular descriptors and reported in Tables 1 and 3. Further, the regression graph was plotted for pIC_{50} vs. \$PRED (Figure 1). A cross-validated correlation coefficient (r^2) value is 0.1084 and root mean square error value is 0.3951. The Z-Score was predicted for all the compounds, wherein a Z-score value of 2.5 and above can be considered to indicate the molecules which are outliers to the fit and showed in Table 3. All the compounds showed significant Z-scores and represented in Table 3. The principal component analysis was carried out using three eigenvalues, viz. PCA1, PCA2 and PCA3, and a 3D graphical plot was generated, which included 98% of the variance and presented. In the plot, all the values were found to lie in the range of 3 to +3 and are shown with different colored spots which correspond to the pIC_{50} of compounds. The result of contingency analysis showed the selected training set for QSAR study was good and all are within the standard limit as suggested. The value of C (contingency coefficient) should be above 0.6, V (Cramer's V) should be above 0.2, U (entropic uncertainty) should be above 0.2 and R (linear Correlation) should be above 0.2., then only this contingency analysis is considered as useful (Table 4).

Table 3: Molecular descriptors, experimental and predicted pIC_{50} (μM) values of 26 naphthoquinone derivatives on QSAR study

S. No.	log P(o/w)	DM	EELE	HOMO	LUMO	MR	TPSA	\$RES	\$Z-SCORE
1	0.814	1.9141	-261336.29	-10.3647	-1.2656	4.5044	46.67	0.3775	0.9555
2	1.057	2.0434	-254694.87	-9.1754	-1.3324	4.8214	60.16	0.0272	0.069
3	2.631	1.8422	-378579.96	-9.1481	-1.2291	6.5132	49.93	-0.3503	0.8866
4	3.363	4.6168	-466949.78	-8.9827	-1.2181	7.4459	49.93	-0.7006	1.7732
5	1.893	0.4905	-345145.06	-9.5863	-1.5212	5.8623	47.28	0.0521	0.1318
6	2.368	0.4806	-382014.4	-9.6079	-1.5113	6.3454	47.28	-0.148	0.3745
7	3.252	0.4578	-461026.59	-9.5739	-1.5047	7.2918	47.28	-0.1918	0.4855

8	3.252	5.3749	-464380.9	-9.0448	-1.4934	7.2918	47.28	0.1779	0.4533
9	1.679	1.0067	-309412.93	-9.9066	-1.5734	5.4049	47.28	0.4317	1.0926
10	1.804	1.5618	-532032.37	-9.8753	-1.6027	7.0209	69.67	-0.4922	1.2457
11	1.448	3.618	-412647.62	-10.14	-1.8255	6.4016	64.35	0.5448	1.3788
12	2.638	0.8638	-473690.46	-9.6289	-1.5011	7.15	43.37	-0.284	0.7189
13	2.638	5.3298	-475680	-9.2366	-1.4684	7.15	43.37	-0.3236	0.8198
14	3.313	1.0199	-509260.62	-9.6489	-1.5574	7.8897	43.37	-0.4005	1.0135
15	3.313	5.0389	-511396.96	-9.2955	-1.5167	7.8897	43.37	-0.0917	0.2321
16	2.999	4.9787	-501379.15	-9.2375	-1.4231	7.1658	43.37	-0.1672	0.4232
17	2.594	5.1465	-420172.9	-9.2339	-1.4486	6.7043	43.37	-0.7598	1.9229
18	1.393	4.0727	-449597.93	-10.3699	-2.0563	7.1081	73.33	0.0164	0.0416
19	1.773	3.7769	-589837	-9.7466	-1.7513	8.1776	67.59	0.5468	1.3839
20	3.145	3.0897	-579448.93	-9.5721	-1.6489	8.9661	71.44	0.7491	1.8959
21	3.178	4.0484	-629022.62	-9.8442	-1.7286	9.2554	54.45	0.0831	0.2103
22	3.181	2.2871	-588681.93	-9.953	-1.9288	8.8964	73.06	0.4877	1.2344
23	1.221	1.9162	-299093.59	-10.3269	-1.2336	4.9463	46.67	-0.3988	1.0093
24	2.43	2.0416	-291737.53	-10.2644	-1.6684	5.468	34.14	0.3268	0.8271
25	1.893	5.0365	-345632.93	-9.0559	-1.509	5.8623	47.28	0.3752	0.9497
26	2.368	5.3418	-382822.84	-9.0674	-1.5019	6.3454	47.28	0.112	0.2834

logP (o/w): Log octanol/water partition coefficient, DM: Dipole Moment, EEL: Electrostatic Interactions, LUMO: Lowest Unoccupied Molecular Orbital, HOMO: Highest Unoccupied Molecular Orbital, MR: Molecular Refractivity, TPSA: Topological Polar Surface Area, pMIC: Experimentally calculated log MIC, \$PRED, \$RES and \$Z-SCORE: Predicted pMIC, residual and Z-score values.

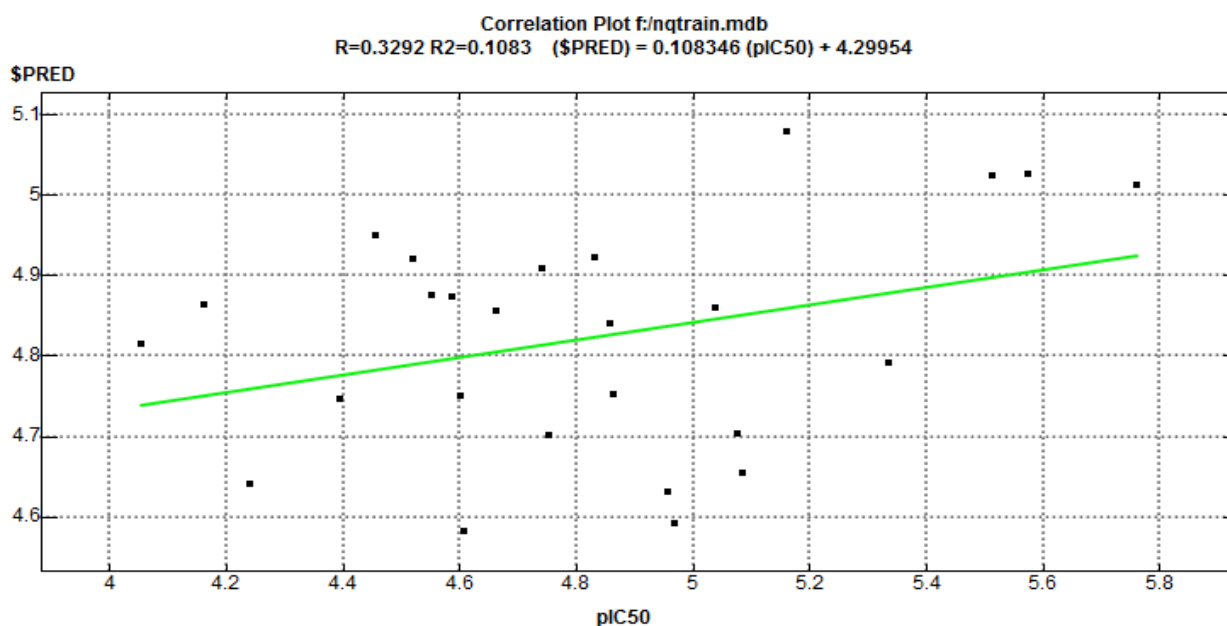


Figure 1: Fitness graph between observed and predicted binding affinity for training set compounds

Linear correlation graph of experimentally measured pIC₅₀ values of training set of 26 compounds against HT-29 cell. The linearity of QSAR model was shown with error value (RMSE) and correlation actor (R2).

Table 4: QSAR contingency analysis (database fields and suggested descriptors for QSAR)

S. No.	C	V	U	R	Field
1	0.88999	0.56345	0.60034	0.04106	AM1_dipole
2	0.89733	0.58689	0.62631	0.10835	AM1_Eele
3	0.88778	0.55682	0.57275	0.07167	AM1_HOMO
4	0.91107	0.63798	0.66639	0.39767	AM1_LUMO
5	0.85895	0.48424	0.48087	0.00009	logP(o/w)
6	0.88962	0.56232	0.58463	0.13165	mr
7	0.89103	0.56663	0.57166	0.25166	TPSA
8	0.88976	0.56273	0.60317	0.10835	\$PRED

9	0.91636	0.66076	0.73938	0.89165	\$RES
10	0.88723	0.55517	0.61793	0.00411	\$Z-SCORE
11	0.86317	0.4935	0.54812	0.0082	\$XPRED
12	0.91619	0.65997	0.73882	0.89665	\$XRES
13	0.90532	0.61531	0.62016	0.01249	\$XZ-SCORE

C: Contingency Coefficient (above 0.6 is useful); V: Cramer's V (above 0.2 is useful); U: Entropic Uncertainty (above 0.2 is useful); R: Linear Correlation (above 0.2 is useful)

The Predicted activity of newly designed NQ derivatives

Using the trainpred fit file obtained from the above training set QSAR model, we can evaluate the predicted pIC₅₀ values for the test set containing 20 compounds i.e. for the newly designed NQ derivatives. These new molecules were digitized, optimized and aligned using the same methodology described for the experimental QSAR analysis, and found that these were showed an improved theoretical anti-cancer activity against HT-29 cells and the predicted activity were represented in Table 5. However, from this QSAR study, the newly designed 20 compounds were shown a better activity as compared with the reported pIC₅₀ values except for the compound no L14, which does not show any biological activity. It may be due to the presence of indoline moiety with this structure, where the more electronegative two oxygen atoms are present at nearby position at 2, 3 of indoline ring, while in compound no L12 contains an isoindoline ring instead of indoline ring, where the two oxygen atom present at position 1 and 4 of isoindoline ring and showed a better activity when compared to the reported experimental data.

Table 5: Predicted cytotoxic activity for the newly designed structures using the QSAR model

Compound	pIC ₅₀ Predicted	Compound	pIC ₅₀ Predicted
L1	5.0306	L 11	4.7917
L 2	5.2199	L 12	5.0924
L 3	5.0878	L 13	5.2025
L 4	4.857	L 14	-
L 5	5.0471	L 15	5.0696
L 6	4.7691	L 16	5.0925
L 7	5.1943	L 17	4.9788
L 8	4.8432	L 18	4.8949
L 9	5.1869	L 19	5.0885
L 10	5.2531	L 20	5.0041

CONCLUSION

A cross-validated correlation coefficient (r^2) value is 0.1084 and root mean square error value is 0.3951. Moreover, all the compounds showed significant \$Z-scores and lies within the limit. The result of principal component analysis and contingency analysis showed the selected training set for QSAR study was good and all are within the standard limit as suggested in the literature. The QSAR studies on these compounds have been shown that the predicted pIC₅₀ values of the compounds have an acceptable correlation with the experimental values from the generated regression, principal component analysis (PCA) plots and from the contingency analysis.

Quantitative structure activity relationship studies revealed that the anticancer activities of these NQ derivatives against the cancer cell are mainly governed by log P value, dipole moment, HOMO, LUMO, the molar refractivity, and a steric parameter. Thus a proper substitution of the group on quinine ring probably improves the effectiveness of these derivatives as anticancer agents. In conclusion, QSAR model generated from the present study should be useful for designing the similar group of more potent substituted compounds with nitrogen, sulphur and oxygen atoms as promising anticancer agents. However, from this QSAR study, the newly designed 20 compounds were shown a better activity as compared with the reported IC₅₀ values except for the compound no L14, which contains an indoline ring with two electronegative oxygen atoms at position 2 and 3 of indoline ring structure and did not show any biological activity.

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