Nat. Volatiles & Essent. Oils, 2021; 8(6): 5082-5097

NVEO
Natural Volatiles &
Essential Oils

Quantitative Structure-Activity Relationship Study Of Coumarin Pyrazoline Hybrid With Sulfamoyl Moiety As Anti-Cancer Agents

T. Prabha*[1], E. Manickavalli[1] , S. Sri Bhuvaneswari[2] , K. Menaka[1] , G. Kiruthika[1], CN Marimuthu[3]

[1]Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Erode-638052, Tamilnadu, India

[2]Department of Pharmaceutical Biotechnology, Nandha College of Pharmacy, Erode-638052, Tamilnadu, India

[3]Nandha Engineering College, Erode-638052, Tamilnadu, India

Abstract

A set of coumarin pyrazoline linked with sulphonamide analogues were created for prospective "LEAD"s as anti-cancer activity. The rising cancer burden, coupled with population increase, as well as the altering occurrence of various cancers connected to social and economic development, medication tolerance, and other factors, all contribute to the quest for novel chemotherapeutic drugs. A quantitative structure-activity relationship study is conducted out to further investigate the efficacy of the developed coumarin pyrazoline linked with sulphonamide analogues. A QSAR method using known coumarin sulphonamide analogues against the HeLa cell was examined to build a novel druggable model for the suppression of cancer cell growth. The QSAR models were developed using multiple linear regression analysis and then validated both internally and externally for activity prediction. For 20 coumarin sulphonamide analogues, an exact MIC values (g/ml) were obtained and matched with additional descriptor variables such as log p (o/w), MR, apol, ASA+, ASA-, and TPSA. A cross-validated coefficient of correlation (r2) was obtained as 0.47526 and a root mean square error (RMSE) of 0.33069 was obtained from the training set of 20 analogues. Furthermore, using the trainpred.fit file from the Molecular Operating Environment 2009.10 software, we have theoretically approximated the expected pIC50 for the newly developed test set, which consists of six coumarin pyrazoline linked with sulphonamide analogues, relying on this QSAR analysis. The current study's QSAR model might be beneficial in the development of a comparable set of analogues as anti-cancer drugs.

Keywords: QSAR, Coumarin, Sulphonamide derivatives, Molecular descriptors, Anti-cancer activity.

INTRODUCTION

Cancer has become a serious threat to human health. Owing to the diverse factors like population growth, aging, presence of drug resistance, etc. The incidence of cancer is increasing currently, necessitating the development of innovative chemotherapeutic drugs with a distinct structure and a mode of action that is perhaps distinct from that of existing medications in order to combat the threat [1].

Coumarins were considered because their analogues are widely found in natural sources and have a bioactivities, including antibacterial, antioxidant, anti-inflammatory, and anticancer properties [2-4]. The incorporation of the acyl hydrazones ring, which has been extensively exploited in the construction of novel bioactive substances with noteworthy pharmacological properties, notably anti-cancer action [5,6]. Coumarins can act on tumour cells through a variety of mechanisms, including DNA intercalating agents, DNA cross-linking agents, inhibition of the telomerase enzyme, topoisomerase, inhibition of protein kinases, and decreased expression of oncogene expression, or by detaining the cell cycle in G0/G1 phase, G2 /M phase, based on their structure [7]. Moreover, 7-methoxy-8-isopentenyl coumarin, showed potent activity against lung cancer A549 cells and breast cancer cells by arresting the cell cycle in G2 phase followed by inducing apoptosis through modulating PI3K/Akt pathway [8]. Novel coumarin 3-(N-aryl) sulfonamides, displayed considerable growth inhibition followed by cell death in different cancer cell lines with GI50 values less than 100 µM and proved to be activators of JNK1 alpha protein kinase [9]. Equally, the pyrazolines have been largely studied recently owing to their pharmacological activities [10], which includes anti-tumor [11], anti-tubercular [12], anti-inflammatory [13], anti-parasitary [14], anti-depressive, anticonvulsant [15], antimicrobial [16], antinociceptives [17], antifungal [18], antioxidant [19], and nitric oxide synthase inhibitors, associated with diseases such as Alzheimer, and inflammatory arthritis [20,21].

In recent times, the molecular hybridization approach has emerged as a novel approach for developing prototype multifunctional compounds that involves the arrangement of two or more pharmacophores in one molecular scaffold. Due to the mixing of pharmacophores in one compound, such compounds offer a wide range of biological actions and may be further adjusted to have good pharmacokinetics and increased bioavailability. Several researchers used this method to develop and synthesise the numerous hybrid structures. Hybridization or pairing of various coumarin derivatives with various biomolecules such as sulfonamides, pyrazoline, chalcone, triazoles, and other biomolecules has resulted in new hybrid molecules with vasorelaxant, platelet anti-aggregating, anticancer [22], monoamine oxidase-B (MAO-B) inhibiting, antimicrobial, antioxidant, and anti-inflammatory characteristics. As a consequence, the molecular hybridization method is being used to produce new compounds for the treatment of a variety of complicated disorders. In addition, by combining the coumarin ring with additional heterocyclic functionalities, novel compounds with better anticancer potential profiles are created [23]. The antimicrobial, antibacterial, anticancer (DNA cleavage), human monoamine oxidase suppressive, antioxidant, and anticholinesterase properties of 3- and 4-heteroarylcoumarins have indeed been documented in recent years. The heterocyclic molecule linked pyrazoline moiety, on the other hand, have a strong therapeutic effect and might be coupled with

coumarin to demonstrate cytotoxic effects. Coumarin compounds with a 4,5-dihydro pyrazole group, have a strong antitumor activity [24,25].

Quantitative structure - activity research has been recognized as a key tool in the development of innovative medication alternatives in a range of treatment domains [26]. It contributes to the development of a statistical model that can quantitatively forecast the behavior of unproven substances by providing valuable clues into the structural aspects that are essential for bioactivity. The Quantitative structure - activity method is used to determine structural factors of functional groups including such lipophilicity, polarizability, electronic, and steric properties, among others, for enhanced biological properties, resulting in the construction of a unique chemical structure with enhanced pharmacokinetics and pharmacodynamics properties [27,28]. Once a link involving structural feature and functionality is established, any range of compounds, even ones that have not yet been synthesized bioactivity are predicted [29].

Furthermore, we decided to analyze the activity of the compounds using various multivariate statistical method such as principle component analysis (PCA) and contingency analysis (CA) that are being used to categorise compounds based on their biological activities and the variability of the fingerprints (i.e. descriptors). The descriptors selection module were used to choose the descriptors that would be utilized as input variables for multiple linear regressions and cross-validation of the model performance. This research has brought a renewed interest in identifying potential anticancer compounds with unique mechanisms of action in drug discovery and development pipelines [29].

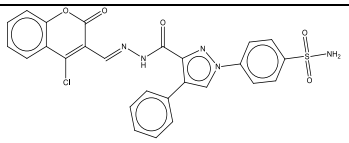
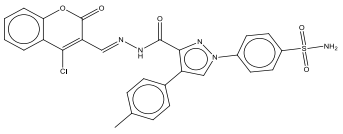
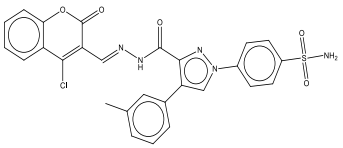
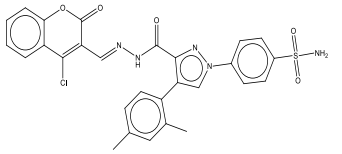
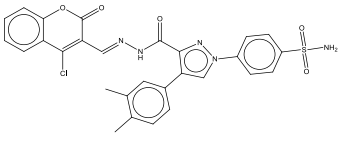
In this regard, we employed in-silico analysis to create a series of coumarin pyrazoline coupled with sulphonamide analogues as strong anticancer drugs. We conduct a QSAR research utilizing the Molecular Operating Environment 2009.10. computational package to further examine the efficacy of these compounds as part of a lead optimization effort. This study recommends that, a QSAR model should be built using multiple regression approaches to investigate the substitution pattern for coumarin pyrazoline coupled with sulphonamide analogues, which is critical for improving anticancer effectiveness.

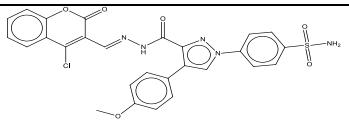
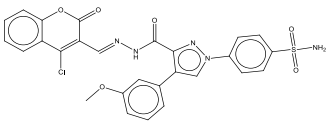
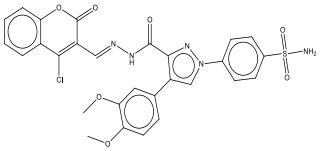
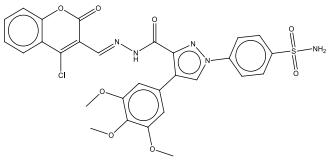
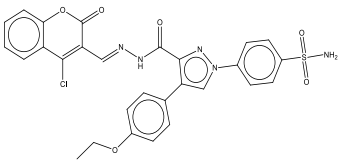
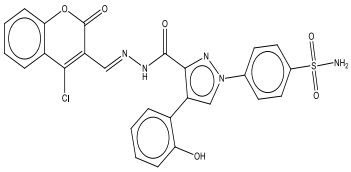
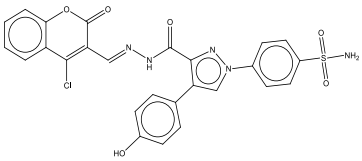
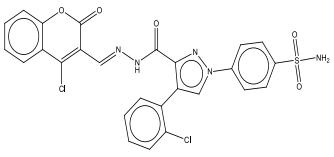
EXPERIMENTAL

The half-maximal inhibitory concentration (IC50) is an indicator of a substance's ability to inhibit a certain biological or metabolic activity into at least 50%. Using the formula pIC50 = -log IC50, the IC50 values were manually transformed into pIC50 (predicted IC50). A total of twenty compounds were chosen from the reported earlier literature for building of QSAR models of coumarin sulfonamides analogues. The dependent variable was biological activity, while the independent variables of approximately six molecular descriptors were chosen for our study. Moreover, internal and external validation processes were used to validate the compounds in the dataset [29].

Dataset: Thus, in this study, we have selected a series of 20 coumarin sulfonamides derivatives that were previously synthesized [6] and all of them were investigated for their anti-cancer activity against HeLa cells. Twenty-six compounds were taken into a data set, where the twenty already reported compounds were assigned as a training set and the remaining six designed compounds were taken as the test set. An attempt was made to establish a QSAR correlation between cytotoxicity activity against HeLa cells and with the series of twenty coumarin sulfonamides analogs was performed by using multiple linear regression analysis. The structures of the training set of the twenty coumarin sulfonamides derivatives were represented in Table 1. The IC_{50} (μM) values were first converted into a negative logarithmic scale (pIC_{50}) to achieve the normal distribution [30] (Table 2). The biological data used in this study were IC_{50} values of coumarin sulfonamides derivatives possessing cytotoxicity activity against HeLa cells.

TABLE 1 CHEMICAL STRUCTURES OF 20 COUMARIN SULFONAMIDES DERIVATIVES USED IN THE TRAINING SET

S. No:	code	Chemical Structure	Chemical Name
1	7a		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-phenyl-1H-pyrazol-1-yl)benzenesulfonamide
2	7b		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(p-tolyl)-1H-pyrazol-1-yl)benzenesulfonamide
3	7c		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(m-tolyl)-1H-pyrazol-1-yl)benzenesulfonamide
4	7d		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(2,4-dimethylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
5	7e		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(3,4-dimethylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

6	7f		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
7	7g		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(3-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
8	7h		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
9	7i		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
10	7j		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(4-ethoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
11	7k		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(2-hydroxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
12	7l		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(4-hydroxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
13	7m		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(2-chlorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide

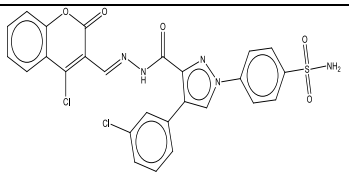
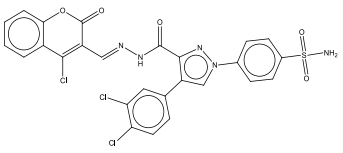
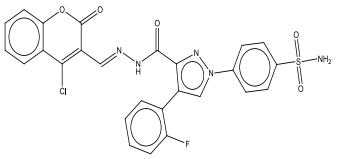
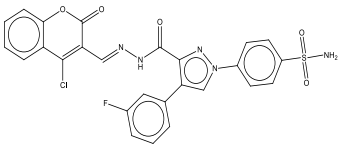
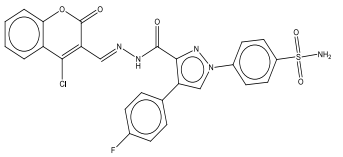
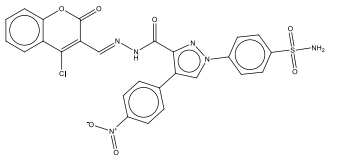
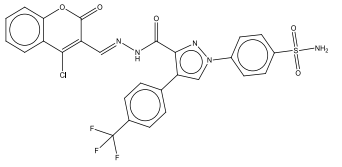
14	7n		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(3-chlorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide
15	7o		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(3,4-dichlorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide
16	7p		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(2-fluorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide
17	7q		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(3-fluorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide
18	7r		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(4-fluorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide
19	7s		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide
20	7t		(E)-4-(3-(2-((4-chloro-2-oxo-2H-chromen-3-yl)methylene)hydrazinecarbonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)benzenesulfonamide

TABLE 2 TRAINING SET COMPOUNDS WITH THE OBSERVED AND PREDICTED CYTOTOXICITY ACTIVITY OF COUMARIN SULFONAMIDES DERIVATIVES

No.	Code	IC_{50}(μM)	pIC_{50}(μM)

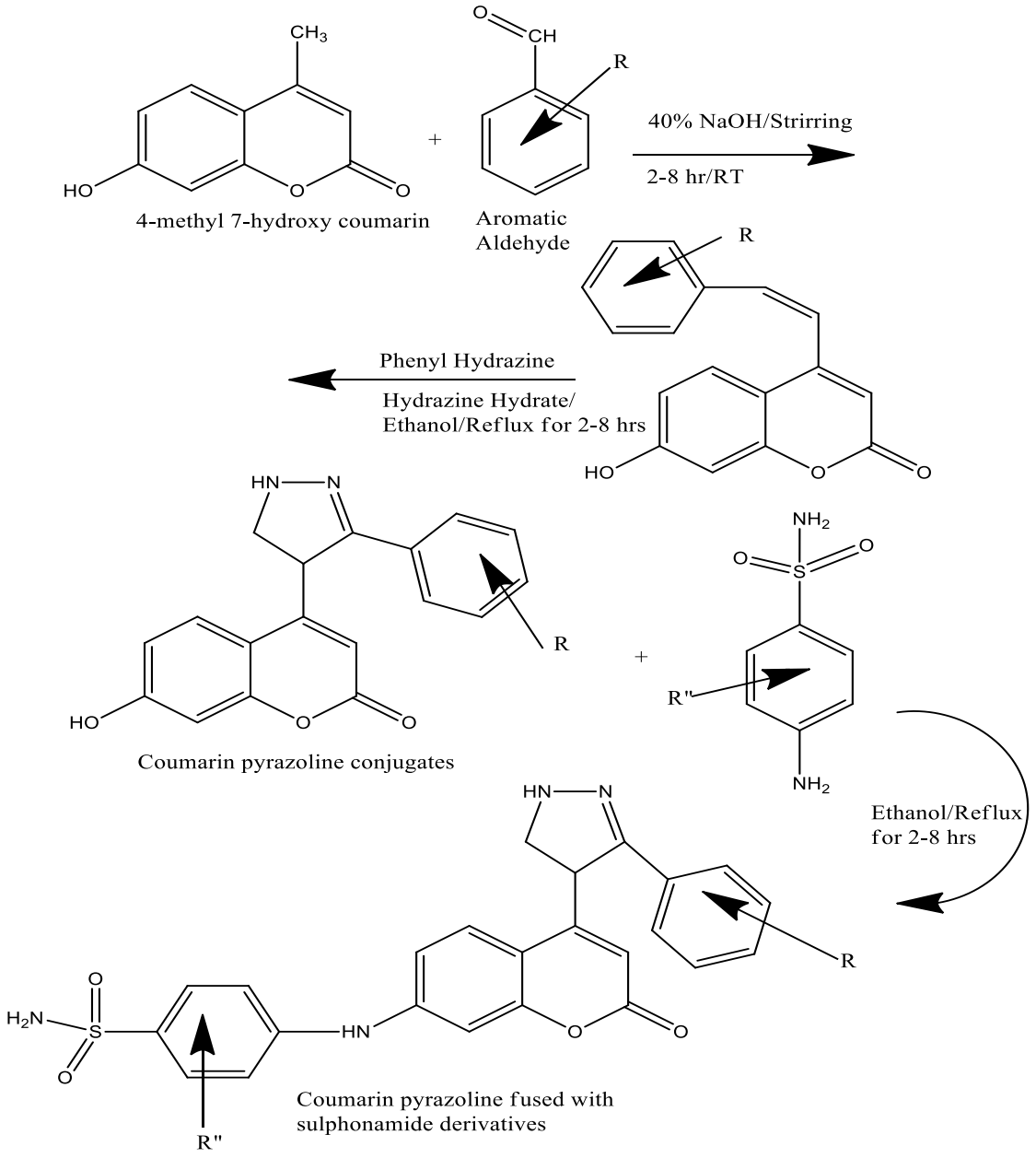
			Observed	Predicted	Residual
1	7a	9.86±0.76	5.006	5.2861	-0.2801
2	7b	8.81±0.73	5.055	4.9673	0.0877
3	7c	11.08±0.86	4.955	5.0166	-0.0616
4	7d	7.95±0.51	5.099	5.3780	-0.2790
5	7e	6.92±0.54	5.158	4.8567	0.3013
6	7f	12.02±1.02	4.92	4.7292	0.1908
7	7g	7.58±0.63	5.12	5.0203	0.0997
8	7h	13.12±1.12	4.882	5.1848	-0.3028
9	7i	16.19±1.26	4.791	5.0465	-0.2555
10	7j	8.76±0.82	5.057	4.8839	0.1731
11	7k	11.67±0.98	4.933	5.4830	-0.5500
12	7l	12.43±1.14	4.906	4.9296	-0.0236
13	7m	5.09±0.35	5.293	5.5584	-0.2654
14	7n	5.46±0.39	5.263	5.7028	-0.4398
15	7o	4.91±0.51	5.309	5.4697	-0.167
16	7p	2.85±0.27	5.545	5.4618	0.0832
17	7q	3.43±0.42	5.465	5.5727	-0.1077
18	7r	0.94±0.12	6.027	5.5321	0.4949
19	7s	0.52±0.09	6.284	5.6307	0.6533
20	7t	0.36±0.05	6.444	5.8019	0.6421

Molecular descriptors: Partition coefficients, molar refractivity, the sum of the atomic polarizabilities, positive solvent-accessible surface area, negative solvent-accessible surface area, and topological polar surface area were selected as descriptors in this QSAR analysis to define the structure of the compounds comprising the series to be studied [29].

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 twenty coumarin sulphonamide derivatives with their cytotoxicity activity [6]. For the aforementioned compounds, the QSAR model was built using six molecular fingerprints (descriptors) from the inbuilt QSAR descriptor module. In the activity fields, the experimentally determined pIC50 (μM) for the twenty coumarin sulphonamide analogues against HeLa cells were carefully entered. The RMSE and R2 values were generated from the QSAR fit during the regression study. For each of the aforementioned twenty compounds, a QSAR correlation plot was created by graphing the pIC50 values on the x-axis and the predicted values ($PRED) on the y-axis. In addition, in order to recognize the active compounds in the data set, the "QSAR Contingency" program was deployed, proceeded by principal component analysis (PCA) and plotted a 3D graphical scatter graph with three scalar values [31].

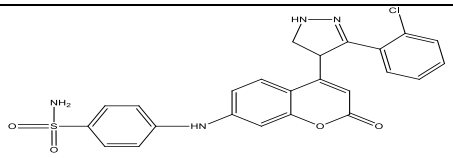
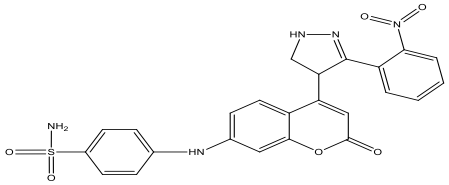
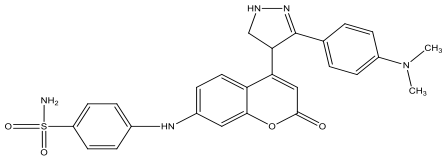
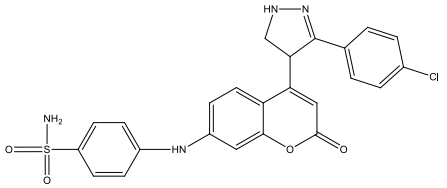
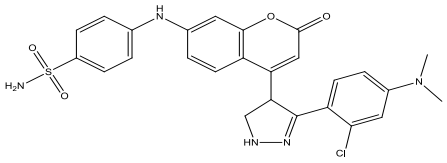
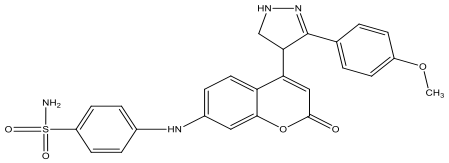
Prediction of cytotoxicity activity of the designed coumarin pyrazoline fused with sulphonamide derivatives: Based on the results of the above-generated 3D-QSAR model, we identified the key structural features for improving the cytotoxicity potency of the newly designed coumarin pyrazoline fused with sulphonamide moieties (Scheme 1) (Table 3), which is used as a test set in this QSAR study. Hence, in this study, we have investigated the newly synthesized pyrazoline derivatives containing nitrogen atoms in its structure, for their prediction as potential anti-cancer agents with the help of in-silico 3D-QSAR study.

SCHEME 1 PROPOSED SYNTHETIC SCHEME OF COUMARIN PYRAZOLINE FUSED WITH SULPHONAMIDE DERIVATIVES



Substitution pattern for R= CPS1: 2- Chloro benzaldehyde; CPS2: 4- Chloro benzaldehyde; CPS3: P-dimethyl amino benzaldehyde; CPS4: 2-Chloro, 4-dimethyl amino benzaldehyde; CPS5: Nitro benzaldehyde; CPS6: Anisaldehyde.

TABLE 3 DESIGNED COUMARIN PYRAZOLINE SULPHONAMIDE DERIVATIVES FOR QSAR STUDY

Compound Code	Chemical Structure	Chemical Name
CPS1		4-((4-(3-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-oxo-2H-chromen-7-yl)amino)benzenesulfonamide
CPS2		4-((4-(3-(2-nitrophenyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-oxo-2H-chromen-7-yl)amino)benzenesulfonamide
CPS3		4-((4-(3-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-oxo-2H-chromen-7-yl)amino)benzenesulfonamide
CPS4		4-((4-(3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-oxo-2H-chromen-7-yl)amino)benzenesulfonamide
CPS5		4-((4-(3-(2-chloro-4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-oxo-2H-chromen-7-yl)amino)benzenesulfonamide
CPS6		4-((4-(3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-oxo-2H-chromen-7-yl)amino)benzenesulfonamide

RESULT AND DISCUSSION

For the purpose of model construction, training sets of twenty compounds were submitted to linear free energy regression analysis. Correlation analysis was used to do initial assessment to check the

multicollinearity between the selected descriptors. Table 4 shows the connection coefficients of several chemical descriptors with cytotoxicity activity. Multiple linear regressions produced a QSAR model with a strong correlation between bioactivity and its properties. All of the components in the QSAR model have a favorable association with the descriptors. The positive coefficients indicate that combining such composite structures results in a boost in bioactivity. Table 4 shows the calculated molecular descriptors and anticipated biological activities (pIC50) of the training set.

The QSAR model built with previously reported compounds using experimental results of pIC50 (μM) values to validate the cytotoxicity activities, and the model predicted pIC50, $PRED, and all other known molecular descriptors, as shown in Tables 2 and 4. The regression plot for pIC50 vs. $PRED was also shown in Figure 1. From this model, the obtained RMSE is 0.33069, and the correlation coefficient (r2) is 0.47526. The Z-Score was calculated for all of the compounds and was within the acceptable range, with a Z-score of 2.5 and higher indicating compounds that are outliers to the fit, as shown in Table 4. Table 4 shows that all of the compounds had substantial Z-scores. The principal component analysis was performed with three eigenvalues, PCA1, PCA2, and PCA3, and a 3D graphical representation was created that encompassed 98 % of the variance (Fig. 2). All of the values on the plot were determined to be in the range of 3 to +3 and were represented by distinct colored spots that corresponded to the compounds' pIC50 (Fig. 2).

TABLE 4: EXPERIMENTAL AND PREDICTED PIC50 (μM) VALUES OF TRAINING SET ALONG WITH MOLECULAR DESCRIPTORS

Code	apol	ASA+	ASA-	Log p(o/w)	MR	TPSA	$Z-Score
7a	72.3523	347.8551	384.3672	4.4210	14.2400	145.7300	0.8472
7b	75.4459	385.2640	392.1573	4.7190	14.6996	145.7400	0.2652
7c	75.4459	360.9393	351.6537	4.7560	14.6996	145.7400	0.1862
7d	78.5394	331.3361	357.2171	5.0520	15.1610	145.7400	0.8437
7e	76.2479	368.0295	360.5549	4.3770	14.8874	154.9700	0.9112
7f	76.2479	348.4573	294.6278	4.4140	14.8874	154.9700	0.5770
7g	84.0390	314.8996	322.4230	3.8625	16.1800	173.4300	0.3014
7h	79.3414	332.6211	354.6478	4.7180	15.3649	154.9700	0.9155
7i	73.1543	368.3296	377.4315	4.1110	14.3718	165.9700	0.7727
7j	73.8655	367.7613	453.7794	5.0110	14.7144	145.7400	0.5236

7k	73.8655	257.9366	344.2723	5.0500	14.7104	145.7400	1.6632
7l	75.3787	274.8299	371.4733	5.6400	15.1718	145.7400	0.0715
7m	72.2425	253.2533	281.8685	4.6110	14.3107	145.7400	0.8024
7n	72.2425	271.2312	347.8785	4.5740	14.3107	145.7400	1.3299
7o	74.3895	296.3006	382.5073	4.3560	14.7323	191.5600	0.4858
7p	78.5394	313.8282	337.6754	5.0520	15.1610	145.7400	0.2517
7q	80.1434	256.2489	292.1136	4.1197	15.5353	164.2000	0.3257
7r	73.1543	275.6206	280.6768	4.1130	14.3681	165.9700	1.4964
7s	72.2425	258.9880	309.7993	4.5720	14.3144	145.7400	1.9756
7t	75.1165	278.8322	424.0653	5.3558	14.8407	145.7400	1.9416

Note: apol stands for the sum of atomic polarizabilities. ASA+ denotes a positive solvent-accessible surface area, ASA- denotes a negative solvent-accessible surface area, logP (o/w) stands for Log octanal/water partition coefficient, MR stands for molecular refractivity. Topological polar surface area (TPSA) is a term used to describe the topology of a polar surface. $Z-Score: values for anticipated pIC50, residual, and Z-score.

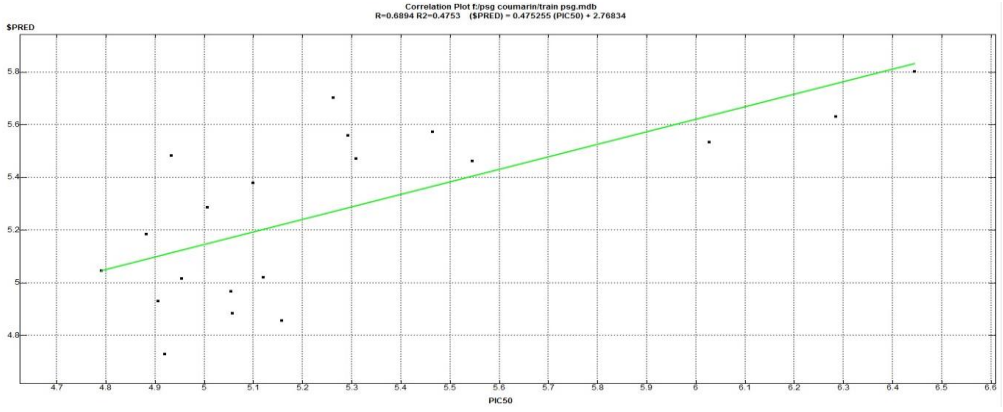


Figure 1: Shows the relationship between observed and anticipated binding affinity for compounds in the training set against HeLa cell.

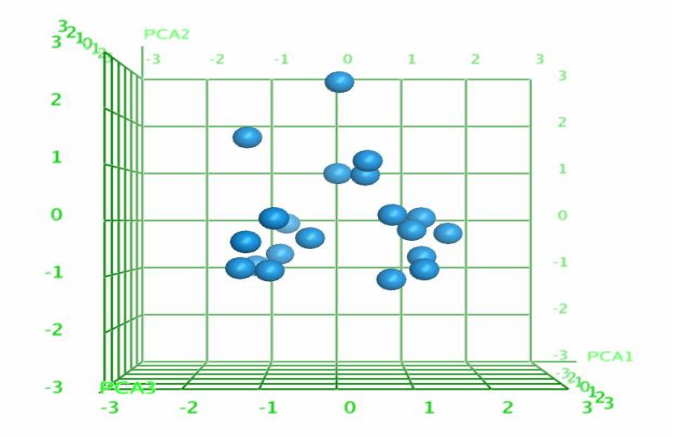


Figure 2: Principal component analysis

The 3D graphical plot was built using three eigenvectors PCA1, PCA2, and PCA3 in the range of 3 to +3, and the coordinate value of each component is indicated by a colored spot in the PCA plot of these compounds.

The chosen data set for the QSAR investigation was acceptable, and all were within the specified range, as shown by contingency analysis (Table 5). Only if the value of 'C' (contingency coefficient) is more than 0. 6, 'V' (Cramer's V) is greater than 0.2, 'U' (entropic uncertainty) is greater than 0.2, and 'R' (linear correlation) is greater than 0.2, then this contingency analysis has been considered as effective one (Table 5).

Table 5: Result of contingency analysis

Code	Contingency Coefficient (C)	Cramer's (V)	Entropic Uncertainty (U)	Linear Correlation (R)	Field
1	0.77799	0.35746	0.39916	0.02704	apol
2	0.82616	0.42328	0.48890	0.27660	ASA+
3	0.87332	0.51752	0.51466	0.02291	ASA-
4	0.85646	0.47896	0.49550	0.00186	logP(o/w)
5	0.79047	0.37255	0.40125	0.02953	mr
6	0.75525	0.33264	0.35641	0.00028	TPSA
7	0.88546	0.55004	0.55685	0.47526	$PRED
8	0.90766	0.62428	0.64050	0.52474	$RES
9	0.90413	0.61086	0.60704	0.39010	$Z-SCORE
10	0.85317	0.47214	0.54725	0.07444	$XPRED
11	0.90952	0.63165	0.63155	0.46669	$XRES

The proposed coumarin pyrazoline coupled with sulphonamide analogues is expected to possess the cytotoxicity activity:

We can analyze the anticipated pIC_{50} values for the test set including 6 compounds, i.e., for the new entity of coumarin pyrazoline coupled with sulphonamide analogues, by using trainpred.fit file acquired from the aforementioned training set QSAR model. These novel compounds were computerized, refined, and matched using the same methods as described as in the experimental QSAR study, and it was discovered that they had a theoretically increased cytotoxicity impact against HeLa cells, as shown in Table 6. Nevertheless, the newly developed compounds showed superior activity in this QSAR analysis when compared to previously published coumarin sulphonamide derivatives pIC50 values, which might be due to the inclusion of an extra pyrazoline group with in its structure.

TABLE 6 PREDICTED CYTOTOXICITY ACTIVITY FOR THE NEWLY DESIGNED COMPOUNDS

Compound code	pIC_{50} Predicted	Compound code	pIC_{50} Predicted
CPS1	6.5250	**CPS4**	6.7619
CPS2	6.3638	**CPS5**	6.8133
CPS3	6.8302	**CPS6**	6.6340

Conclusion

To explore the potency of the coumarin sulphonamide derivatives, a quantitative structure-activity relationship study was carried out to know the residual difference between observed and predicted cytotoxicity potency of the selected compounds. The results showed a cross-validated correlation coefficient (r2) value was 0.47526 and the root mean square error value was 0.33069 moreover, all the compounds showed significant $Z-scores and lie within the limit of 2.5. The results of principal component analysis and contingency analysis, on the other hand, demonstrated that the training set used for the QSAR analysis was acceptable, and that all of the variables were within the specified range as stated in the literature. The predicted pIC_{50} values of the compounds have an adequate relationship with the experiment data from the computed multiple linear regression, principal component analysis plots, and contingency analysis.

Further, the quantitative structure-activity relationship studies revealed that the cytotoxicity activity of newly designed coumarin pyrazoline linked with sulphonamide moieties against the HeLa cell line was mainly governed by partition coefficient, molar refractivity, and the sum of the atomic polarizabilities, positive solvent-accessible surface area, negative solvent-accessible surface area, and topological polar surface area. As a result, correct replacement of the group on coumarin pyrazoline nuclei and hybrid of two or more active compounds might likely boost the anticancer efficacy of these compounds. Furthermore, the QSAR model developed in this work should be beneficial in the development of a comparable class of more powerful substitution compounds as potential anticancer medicines.

DECLARATIONS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. WHO, Cancer, World Health Organization, https://www.who.int/cancer/PRGlobocanFinal.pdf, February 2018.
2. S. Mehrparvar, S. Balalaie, M. Rabbanizadeh, F. Rominger, and E. Ghabraie, Org. Biomol. Chem., **12**, 5757 (2014).
3. M.A. Musa, J.S. Cooperwood, and M.O.F. Khan, Med. Chem., **26**, 2664 (2008).
4. L. Piazzi, A. Cavalli, F. Colizzi, F. Belluti, M. Bartolini, F. Mancini, M. Recanatini, V. Andrisano, A. Rampa, Bioorg. Med. Chem. Lett., **18**, 423 (2008).
5. N.C. Romeiro, G. Aguirre, P. Hernández, M. González, H. Cerecetto, I. Aldana, S. Pérez-Silanes, A. Monge, E.J. Barreiro, and L.M. Lima, Biorg. Med. Chem., **17,** 641 (2009).
6. X.Y. Lu, Z.C. Wang, S.Z. Ren, F.Q. Shen, R.J. Man, and H.L. Zhu, Bioorg. Med. Chem. Lett., **26**, 3491 (2016).
7. J. Klenkar, and M. Molnar, J. Chem. Pharma. Res., **7**, 1223 (2015).
8. S.J. Kao, J.L. Su, C.K. Chen, M.C. Yu, K.J. Bai, J.H. Chang, M.Y. Bien, S.F. Yang, and M.H. Chien , Toxicol. Appl. Pharmacol., **261**, 105 (2012).
9. N.S. Reddy, M.R. Mallireddigari, S. Cosenza, K. Gumireddy, S.C. Bell, E.P. Reddy, and M.V. Reddy, Bioorg .Med. Chem. Lett.,**14**, 4093 (2004).
10. K. Ishwarbhat, and K. Abhishek, Res. J. Pharm. Tech., **10**, 1344 (2017).
11. M. Johnson, B. Younglove, L. Lee, R. LeBlanc, H. Holt, P. Hills, H. Mackay, T. Brown, L.S. Mooberry, and M. Lee, Bioorg. Med. Chem., **17**, 5897 (2007).
12. S. Prafulla, B. Dhiraj, and S. Vidya, Res. J. Pharm. Tech.,**11**, 3599 (2018).
13. S. Sahu, T. Dey, S. Khaidem, and Y. Jyothi Res. J. Pharm. Tech., **4**, 413 (2011).
14. A.R. Bhat, F. Athar, and A. Azam, Eur. J. Med. Chem., **44**, 926 (2009).
15. Z. Ozdemir, H.B. Kandilci, B.H. Gumusel, U. Calıs, and A.A. Bilgin, Eur. J. Med. Chem., **42**, 373 (2007).
16. Prabha, T, Jubie S, Selvamani, P. Latha S., Sivakumar, T.. (2019). International Journal of Research in Pharmaceutical Sciences. 10(4), 3159-3169.
17. S. Kulveer, K. Suman, and Y.K. Gupta, Res. J. Pharm. Tech.,**10**, 4483(2017).

18. B.C Revanasiddappa, M. Vijay Kumar, N. Prashanth, R.A. Ajmal, and M.S. Jisha, Res. J. Pharm. Tech., **10**, 1481 (2017).

19. K. Ishwar Bhat, and K. Abhishek, Res. J. Pharm. Tech., **11**, 1978 (2018).

20. C.L.C. Luisa, C.M. Encarnacio´n, C.M. Dora, V. Tapias, A.G. Miguel, E. Germaine, A.C. Darı´o, E. Antonio, E. Antonio, Eur. J. Med. Chem.,**44**, 2655 (2009).

21. T. Prabha, S. Jubie, P. Selvamani, S. Latha, and T. Sivakumar, Int. J. Res. Pharm. Sci., **10**, 3159 (2019).

22. D.C.G.A. Pinto, and A.M.S. Silva, Med. Chem., **17**, 3190 (2017).

23. A. Anees, Pangal, A. Javed, Shaikh, and M. Ejazuddin Khan, Int. J. Pharm. Sci. Rev. Res., **42**,161 (2017)

24. K.M. Amin, A.A.M. Eissa, S.M. Abou-Seri, F.M. Awadallah, and G.S. Hassan, Eur. J. Med. Chem., **60**, 187 (2013).

25. D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, L. Zaprutko, A. Gzella, and R. Lesyk, Eur. J. Med. Chem.,**44**,1396 (2009).

26. M.T. Chhabria, B.M. Mahajan, and P.S. Brahmkshatriya, Med. Chem. Res., **20,** 1573 (2001).

27. H. Corwin, and F. Toshio, J. Am. Chem. Soc., **86**, 1616 (1964).

28. P. Sivaprakasam, A. Xiea, and R.J. Doerksen, Bioorg. Med. Chem., **14**, 8210 (2006).

29. Prabha, T.; Aishwaryah, P.; Manickavalli, E.; Chandru, R.; Arulbharathi, G.; Anu, A.; Sivakumar, T. A Research J. Pharm.Tech., **2019**, 12(8), 3857-3865.

30. S. Chandrabose, K.T. Sunil, K.R. Karnati, and K.S. Sanjeev, Biotech. Pharm., **5**, 1104 (2011).

31. M.B. Tirumalasetty, S.R. Sivarathri, V.B. Baki, D. Savita, R. Aluru, S. Thirunavakkarasu, and R. Wudayagiri, The Royal Soc. Chem.,**7,** 18277 (2017).