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QSAR and docking studies of α,β-unsaturated carbonyl compounds against human breast adenocarcinoma cell line MCF-7

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RESEARCH ARTICLE

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ABSTRACT

A quantitative structure-activity relationships (QSAR) studies were carried out by correlating activity against human breast adenocarcinoma cell line MCF-7 of series of α,β-unsaturated carbonyl compounds with their physicochemical descriptors using multiple linear regression method. The predictability of the QSAR model was estimated using internal and external predictivity methods. The best QSAR model was selected, having the squared correlation coefficient r^2 = 0.84684, correlation coefficient r = 0.9202, standard deviation s = 0.38484, and cross-validated squared correlation coefficient Q^2 = 0.7621. Model obtained was used to predicted the activity against breast cancer for a set of designed α,β-unsaturated carbonyl compounds (A1-A16). Docking studies was performed for A1-A16 compounds to evaluated their inhibition on c-Met kinase, which has been overexpressed in a number of cancers.

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1. Introduction

Cancer is a group of illness that results from cells in the body growing abnormally. These cells divide and produce new cells in an uncontrolled way that can spread throughout the body and cause damage to essential organs [1]. Despite recent advances in cancer therapy, cancer is still the second leading cause of death after cardiovascular disorders throughout the world [2], and it is projected to be the primary cause of death within the coming years [3].

Breast cancer is the most common type of cancer in women all over the world. Cancerous breast cells have receptors for binding with estrogen and progesterone to stimulate a growth responses [4]. Estrogens control the development and maintenance of the female sex organs, secondary sex characteristics, and mammary glands, as well as certain functions of the uterus and its accessory organs. They are also formed in the placenta in late pregnancy, which increases the spontaneous activity of the uterine muscle and its response to oxytocic drugs [5].

Currently, there is a huge scientific and commercial interest in the discovery of potent, safe and selective anticancer medications. Among the currently identified antitumor agents, enone derivatives represent an important class of molecules that are abundant in edible plants [6].

Quantitative structure activity relationships and quantitative structure property relationship (QSPR) make it possible to predict the activities/properties of a given compound as a function of its molecular substituent. Essentially, new and untested compounds possessing similar molecular features are likewise assumed to also possess similar activities/properties. Several successful QSAR/QSPR models have been published over the years which encompass a wide span of biological and physicochemical properties [7]. This method included data collection, molecular descriptor selection, correlation model development, and finally model evaluation.

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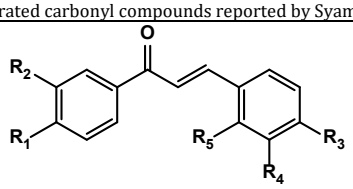
Table 1. Biological activities and structures of α,β-unsaturated carbonyl compounds reported by Syam [9].



Compound	R¹	R²	R³	R⁴	R⁵	IC_{50}	Pc
1	H	H	H	H	H	6.875	5.16
2	CH_3	H	H	H	H	13.62	4.87
3	OCH_3	H	H	H	H	19.15	4.72
4	H	H	H	H	Cl	7.992	5.10
5	OH	H	H	H	Cl	10.01	5.00
6	H	H	H	CH_3	H	9.34	5.03
7	OH	H	H	CH_3	H	8.343	5.08
8	CH_3	H	H	CH_3	H	10.16	4.99
9	OCH_3	H	H	CH_3	H	9.53	5.02
10	H	H	OCH_3	H	H	11.62	4.93
11	CH_3	H	OCH_3	H	H	32.37	4.49
12	OCH_3	H	OCH_3	H	H	41.44	4.38
13	H	H	$N(CH_3)_2$	H	H	99.29	4.00
14	CH_3	H	$N(CH_3)_2$	H	H	57.28	4.24
15	H	H	H	H	OH	9.353	5.03
16	H	CH_3	H	H	OH	6.873	5.16
17	H	OCH_3	H	H	OH	7.149	5.15
18	H	H	H	Cl	H	5.251	5.28

Table 2. Values of molecular descriptors calculated for training set.

ID	FW	MV	ST	MR	E	RI	D	Log P (o/w)
1	208.255	189.8	44.7	67.10	53.88202	1.624	1.097	4.065
2	222.281	206.0	43.2	71.93	56.08740	1.615	1.078	4.363
4	242.700	201.7	46.4	72.00	61.17518	1.632	1.202	4.655
5	238.281	204.5	49.9	73.81	55.46881	1.641	1.165	4.053
6	222.281	206.0	43.2	71.93	56.10360	1.615	1.078	4.400
7	238.281	204.5	49.9	73.81	53.37540	1.641	1.165	4.092
8	236.308	222.3	42.0	76.75	58.28762	1.606	1.062	4.698
9	252.307	230.1	41.8	78.61	65.41583	1.598	1.096	4.356
11	252.307	230.1	41.8	78.61	68.13621	1.598	1.096	4.319
12	268.307	237.8	41.6	80.46	72.26687	1.591	1.128	3.977
13	251.322	227.8	45.9	81.42	72.06151	1.633	1.103	3.980
14	265.349	244.0	44.5	86.24	71.59818	1.624	1.087	4.278
15	224.254	188.2	52.1	68.99	56.14378	1.653	1.191	3.755
16	238.281	204.5	49.9	73.81	58.24109	1.641	1.165	4.090
18	242.700	201.7	46.4	72.00	55.27224	1.632	1.202	4.694

QSAR studies have predictive ability and simultaneously provide deeper insight into mechanism of drug receptor interactions [8].

In the present work, quantitative structure activity relationship study was performed to obtain a QSAR model, which was used to predict the biological activity against human breast adenocarcinoma cell line MCF-7 of a set of designed α,β unsaturated carbonyl compounds (A1-A16). In addition, docking studies was carried out to understand binding interaction between designed compounds (A1-A16) and selected protein 3dkc.

2. Experimental

2.1. QSAR studies

A total of eighteen α,β-unsaturated carbonyl compounds reported by Syam [9] was used in QSAR study. They synthesized several α,β-unsaturated compounds and reported their *in vitro* cytotoxicity against various human cell lines, including human breast adenocarcinoma cell line MCF-7. ChemBioDraw Ultra v14.0.0117 software (Copyright 1998-2014 CambridgeSoft Corporation, a subsidiary of Perkin Elmer, Inc.) was used for drawing series of the studied compounds.

The experimental IC_{50}, concentration of the compounds (IC_{50} in microgram per milliliter) exhibiting 50% inhibition of cell growth for human breast cancer (MCF-7) was converted to negative logarithmic concentration in moles (Pc), values along with the α,β-unsaturated carbonyl structures can be found on Table 1.

The QSAR study was performed using molecular modeling studies of compounds with Molecular Operating Environment software package (MOE, v2010.10; Chemical Computing Group Inc.). A set of 15 compounds was used as a training set for the present QSAR modeling, the three remaining α,β-unsaturated carbonyl compounds chosen randomly were used as an external test set to assess the predictive power of the resulting QSAR model.

2.1.1. Molecular descriptors

Molecular descriptors (physicochemical properties) are chemical information that is encoded within the molecular structures for which numerous sets of algorithms are available for such transformation [7]. Total of eight molecular descriptors namely, formula weight (FW), molar volume (MV), surface tension (ST), molar reactivity (MR), potential energy (E), refractive index (RI), density (D) and Log P (octanol/water) (Log P(o/w)) were calculated for each compound in training set using MOE and ACD/lab (Copyright 1994-2016, ACD/Labs 2016.2, File Version C30E41, Build 90752, 20 Dec 2016) programmes and listed in Table 2.

To select the optimal subset of physicochemical properties, highly correlated chemical descriptors were excluded through covariance analysis using a correlation matrix.

The ratio of the number of compounds to the physicochemical descriptors used for the correlation is usually 5:1 [10].

Table 3. Statistical parameters used for statistical quality of model.

r	r^2	RMSE	Q^2	s	F	*P* value
0.9202	0.84684	0.14550	0.7621	0.38484	101.434	0.010

Table 4. Observed and predicted Pc for training set and cross validation against human breast cancer (MCF-7).

ID	$Pc_{obs.}$	$Pc_{pred.}$	Residuals	$CV_{pred.}$	Residuals
1	5.16	5.051935	0.108065	5.011246	0.148754
2	4.87	5.019001	-0.149000	5.060885	-0.190880
4	5.10	5.087039	0.012961	5.075714	0.024286
5	5.00	5.087764	-0.087760	5.105386	-0.105390
6	5.03	5.029799	0.000202	5.029741	0.000259
7	5.08	5.190366	-0.110370	5.216456	-0.136460
8	4.99	5.002559	-0.012560	5.009727	-0.019730
9	5.02	4.642254	0.377746	4.589873	0.430127
11	4.49	4.513175	-0.023180	4.517511	-0.027510
12	4.38	4.279251	0.100750	4.234203	0.145797
13	4.00	4.249300	-0.249300	4.351688	-0.351690
14	4.24	4.336486	-0.096490	4.367906	-0.127910
15	5.03	5.007334	0.022666	4.992760	0.037240
16	5.16	4.979438	0.180562	4.952883	0.207117
18	5.28	5.354298	-0.074300	5.415618	-0.135620

Table 5. Predicted Pc values of test set.

ID	$Pc_{obs.}$	$Pc_{pred.}$	Residuals
3	4.72	4.66	0.06
10	4.93	4.67	0.26
17	5.15	4.69	0.46

Thus, for the 15 compounds in the training set, only three physicochemical descriptors (D, E, Log P (o/w)) were correlated simultaneously with their breast cancer activity. Lastly, a QSAR model equation was derived by using MLR statistical method (Equation 1). The statistical quality of the regression equations were justified by statistical parameters such as the root mean square error (RMSE), correlation coefficient (*r*), squared correlation coefficient (r^2), standard error of estimate (s) and F-test value (ratio between the variances of observed and calculated activities, F). Calculation of statistical parameters was carried out by using statistical program SPSS version 15.5.

$$Pc = 4.37301 + 1.59035 \times D + 0.31076 \ldots \ldots \times \log P\ (o/w) - 0.04322 \times E \quad (1)$$

In addition, the predictive powers of the equations were validated by the leave-one-out (LOO) cross-validation method (CV). The cross validated squared correlation coefficient (Q^2) was considered for the validation of this model (Table 3).

The developed QSAR model equation showed a relationship between predicted Pc values (-Log IC_{50}) and correlated three chemical descriptors. It is evident from the model equation that the molecular descriptors, namely density and Log (o/w) partition coefficient, are positively correlated. On the other hand, potential energy showed negative correlation.

2.1.2. Validation of quantitative structure-activity relationship model

To test the internal stability and predictive ability of the derived QSAR model, it was validated or cross-checked by the internal validation and external validation test procedure as follows:

(a) Internal validation by training set compounds: This step was carried out by using LOO validation method. For calculating cross validation regression coefficient (Q^2), each molecule in the training set was eliminated once, and the activity of the eliminated molecule was predicted by using the QSAR model developed by the remaining molecules.

(b) External validation by test set compounds: In this step the activity of each molecule in the test set was predicted by using the derived QSAR model developed by the training set compounds [11].

The observed activities and those provided by QSAR studies (Equation 1) for training and test set were presented in Tables 4 and 5. It should be noted that the predicated anticancer activities by obtained QSAR model was close to those experimentally observed, indicating that these model can be safely applied for predication of more effective hits having the same skeletal framework as that of the potent anticancer compound.

2.1.3. Predict the activity of designed α,β-unsaturated carbonyl compounds (A1-16)

A set of designed α,β-unsaturated carbonyl compounds (A1-16) were sketched using the computer software ChemBioDraw program. These compounds were not used in the developed QSAR model, but sketched to predict their anticancer activity against MCF-7 by using developed QSAR model (Equation 1). The predicted activity along with the sketched structures was listed in Table 6.

2.2. Molecular docking

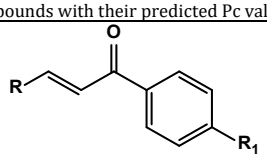
Molecular docking study is a well-established technique to determine the interactions between two molecules (ligand-receptor) and to find the best orientation of ligand that would form a complex with overall minimum energy [12]. It was of interest to perform molecular docking for the designed set (A1-16), in order to understand the ligand–protein interaction in detail. The protein file (PDB ID: 3dkc) selected for this purpose obtained from Protein Data Bank and further optimized and minimized to obtain a low energy and structural correct target protein.

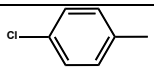
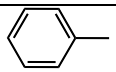
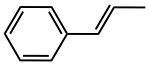
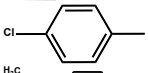
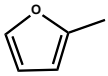
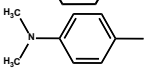
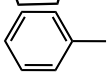
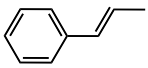
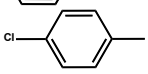
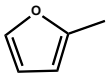
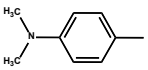
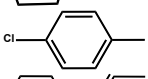
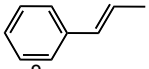
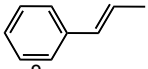
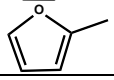
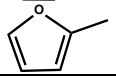
3. Results and discussion

3.1. QSAR studies

Quantitative structure activity relationships studies are useful tools in the rational search for bioactive molecules. The main success of the QSAR method is the possibility to estimate the characteristics of new chemical compounds without the need to synthesize and test them [8].

Table 6. Structures of designed α-β unsaturated carbonyl compounds with their predicted Pc values against human breast cancer (MCF-7).



ID	R	R¹	Predicted Pc	ID	R	R¹	Predicted Pc
A1		-H	5.42	A9		-NO_2	4.47
A2		-H	5.13	A10		-NO_2	4.82
A3		-H	5.12	A11		-NO_2	3.74
A4		-Br	5.75	A12		-NO_2	4.52
A5		-Br	6.08	A13		-NO_2	4.94
A6		-Br	4.99	A14		-CH_3	5.38
A7		-Br	5.77	A15		-CH_3	5.09
A8		-Br	6.24	A16		-CH_3	5.47

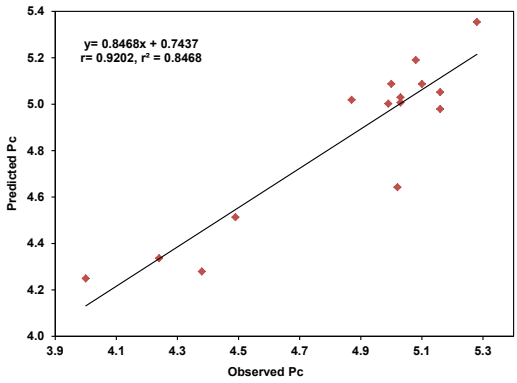


Figure 1. Predicted versus observed Pc values of training set against human breast cancer MCF-7.

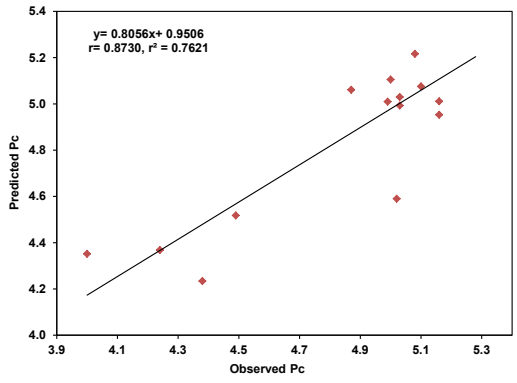


Figure 2. Predicted versus observed Pc values of cross validation against human breast cancer MCF-7.

The resulted QSAR model equation showed a high square of the correlation coefficient (r^2 = 0.84684) and low root mean square error (RMSE = 0.1455), all other statistical parameters calculated to justified the statistical quality of model were in acceptable rang (Table 3).

The predictive ability of QSAR model was validated through leave one out cross validation (Q^2 = 0.7621) and external validation methods. Figures 1, 2 and 3 show the corresponding scatter plots of the observed versus predicted Pc values for the training set, cross validation and test set compounds against breast cancer cell line, respectively.

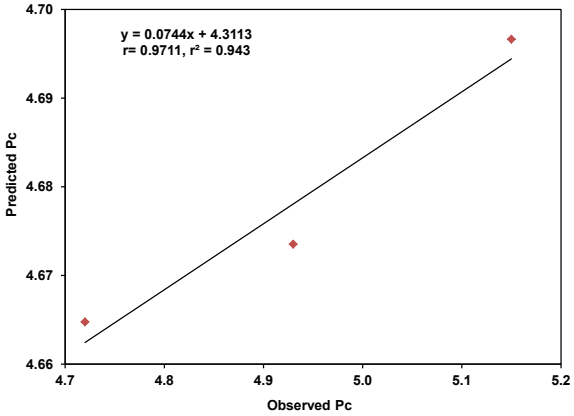


Figure 3. Predicted versus observed Pc values of test set against human breast cancer MCF-7.

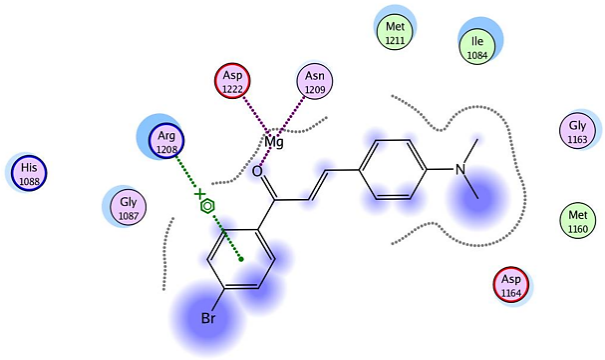


Figure 4. 2D molecular docking model of compound A6 with 3dkc.

Tables 4 and 5 summarize the predicted Pc values of the training set (r^2= 0.8468) and test set (r^2 = 0.9430). QSAR model obtained was used to predict the biological activity of a set of designed α-β unsaturated carbonyl compounds (A1-16) against human breast cancer (MCF-7) Table 6.

It is noteworthy that model equation was derived using the entire data set of compounds (n = 15) and no outliers were identified.

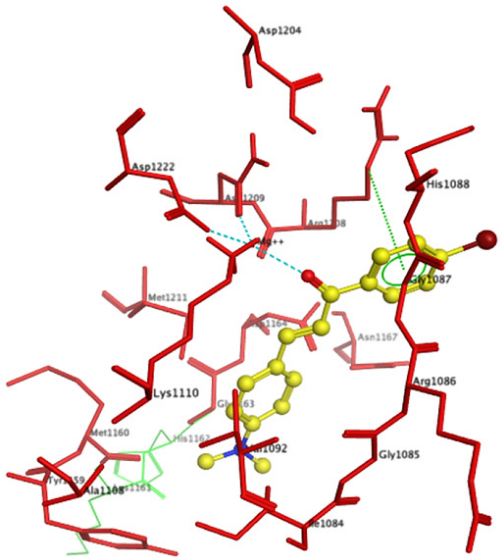


Figure 5. 3D model of the interaction between compound A6 and 3dkc binding site.

3.2. Docking study

A number of human malignancies exhibit sustained stimulation, mutation or gene amplification of the receptor tyrosine kinase human mesenchymal-epithelial transition factor (c-Met) [13]. The overexpression and mutations of c-Met and its natural ligand, hepatocyte growth factor (HGF), have been found in different types of tumors including breast, ovarian, colorectal, lung, gastric, pancreatic, melanoma, prostate, head and neck, glioma, hepatocellular, renal and a number of sarcomas. The 3dkc is the crystal structure of c-Met kinase in complex with ATP which is widely used [14].

Performed molecular docking for all designed α,β-unsaturated carbonyl compounds (A1-16) on the active site of 3dkc may provide an understanding of their effect as antitumor agents. All docking procedures were achieved by MOE (Molecular Operating Environment) software 2010.10.

Molecular docking suggested that all of the designed α,β-unsaturated carbonyl compounds (A1-16) were capable of forming a metal complex with the Mg ion through Asp1222 (bond length 2.10 Å) and Asn1209 (bond length 2.03 Å). Compound A6 showed three interactions, beside two interactions mentioned above, one π-cation interaction was revealed between Arg1208 residue with phenyl ring of 4-bromo benzoyl moiety Figures 4 and 5. Docking score of designed derivatives A1-16 ranging between -22.9170 to -16.1714 kcal/mol. The energy score (S) of the complexes between each designed compounds (A1-16) and the active site of the receptor as well as amino acid interacted are listed in Table 7.

4. Conclusion

From the QSAR studies, it was noticed that the Pc values has been increase in compounds A4-A8 which contain –Br group, compared to the corresponding non-brominated compounds. Compounds A9-A13 which contain $-NO_2$ group showed low Pc values which indicate less activity toward human breast cancer cell line MCF-7. The molecular docking study of A1-A16 compounds has been done for the better understanding of the ligand-receptor interaction and the results confirmed that these compounds were a potential inhibitor of c-Met kinase. In the view of this study, further research can be carried out on designed compounds (A4-A8) to investigate there in vitro anticancer activity against breast cancer.

Table 7. Binding scores and amino acid interactions of the docked designed carbonyl compounds (A1-16) on the active site of 3dkc.

ID	Molecular weight	S (Kcal/mol)	Amino acid interaction	Type of interaction	Length (Å)
A1	242.70	-21.356	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A2	234.29	-21.1818	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A3	198.21	-16.1714	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A4	287.15	-22.9170	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A5	321.59	-20.5912	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A6	330.21	-22.5738	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
			Arg1208	π-cation interaction	-
A7	313.18	-20.6469	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A8	277.11	-22.0121	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A9	253.25	-23.2468	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A10	287.69	-20.7988	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A11	296.32	-23.4193	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A12	279.29	-22.4421	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A13	243.21	-21.7925	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A14	256.72	-20.3991	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A15	248.31	-20.5758	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03
A16	212.24	-22.5230	Asp1222	Metal complex (Mg)	2.10
			Asn1209	Metal complex (Mg)	2.03

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
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