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In silico evaluation and docking studies of pyrazole analogs as potential autophagy modulators against pancreatic cancer cell line MIA PaCa-2

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RESEARCH ARTICLE

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ABSTRACT

A quantitative structure activity relationship (QSAR) model for a series of *N*-(1-benzyl-3,5-dimethyl-1*H*-pyrazole-4-yl) benzamide derivatives having autophagy inhibitory activities as potent anticancer agents was developed by the multiple linear regressions (MLR) method. In this study, previous compounds were used in the model development were divided into a set of fifteen compounds as training set and set of four compounds as test set. A model with high prediction ability and high correlation coefficients was obtained. This model showed r = 0.968, r^2 = 0.937 and Q^2 = 0.880, the QSAR model was also employed to predict the experimental compounds in an external test set, and to predict the activity of a new designed set of 3,5-dimethyl-4-substituted-pyrazole derivatives (1-15), result showed that compound 3 has the most promising inhibition activity (EC_{50} = 0.869 μM) against human pancreatic ductal adenocarcinoma cell MIA PaCa-2 compared to the reference chloroquine with (EC_{50} = 14 μM). Thus, the model showed good correlative and predictive ability. Docking studies was performed for designed compounds, docking analysis showed the best compound 1 with high docking affinity of -24.8616 kcal/mol.

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1. Introduction

Autophagy is a conserved intracellular degradation process that delivers substrates including bulk cytoplasm, organelles, aggregate-prone proteins, and infectious agents to lysosomes [1,2], it is induced under various conditions of cellular stress, which prevents cell damage and promotes survival in the event of energy or nutrient shortage. There are three types of autophagy: macroautophagy [3], microautophagy [4] and Chaperone-mediated autophagy (CMA) [5]. The molecular mechanism of autophagy involves several conserved ATG (autophagy-related) proteins, various stimuli lead to the formation of the phagophore, the elongation of the phagophore results in the formation of the characteristic double-membrane autophagosome. The autophagosome fuses with the lysosome and release its inner compartment into lysosomal lumen, after fusion, a series of acid hydrolases are involved in degradation of the sequestered cytoplasmic cargo. The small molecules resulting from the degradation, particularly amino acids are transported back to the cytosol for protein synthesis and maintenance of cellular functions under starvation conditions [6-9].

In cancer, the role of autophagy is highly complex and dependent on cancer type and stage [10], autophagy has been shown to act as a tumor suppressing to constrains tumor initiation in normal tissue, some tumor in last stage of progression rely on autophagy for tumor promotion and maintenance [11-13]. Therefore, targeting autophagy and discovering autophagy inhibitions and its modulation has considerable potential as anticancer agents used in therapeutic approach, especially in pancreatic ductal adenocarcinoma (PDAC), which it represents a viable approach to fight pancreatic cancer.

Quantitative structure activity relationships is a mathematical equation relating chemical structure with its physical, chemical and biological effect [14], QSAR model is useful for understanding the factors controlling activity and for designing new compounds for therapeutic areas [15-17], it requires a compound set that has been tested against an identified molecular target, cell tissue, or even microorganism,

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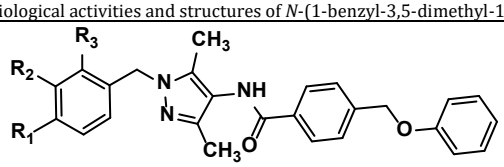
Table 1. Biological activities and structures of *N*-(1-benzyl-3,5-dimethyl-1*H*-pyrazole-4-yl) benzamide compounds obtained from literature [22].



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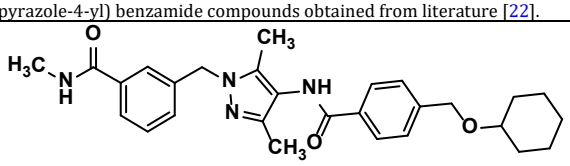

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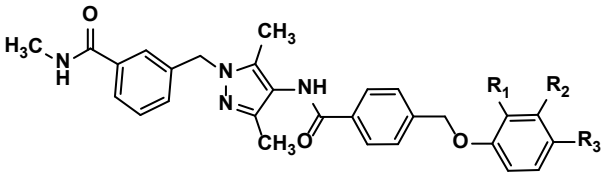


10-19

Compound	R^1	R^2	R^3	EC_{50}	pEC_{50}
1	H	H	H	10.00	5.000
2	H	$C(O)NH_2$	H	9.20	5.036
3	H	H	$C(O)NH_2$	42.00	4.377
4	H	C(O)NHMe	H	6.20	5.208
5	H	$C(O)N(Me)_2$	H	6.40	5.194
6	H	C(O)NHEt	H	11.00	4.959
7	H	$C(O)NH^iPr$	H	8.90	5.051
8	H	C(O)NHPh	H	6.40	5.194
9	-	-		14.00	4.854
10	H	Me	H	6.20	5.208
11	OMe	H	H	8.50	5.071
12	H	OMe	H	6.20	5.208
13	H	H	OMe	8.00	5.097
14	Cl	H	H	6.30	5.201
15	H	Cl	H	5.90	5.229
16	H	H	Cl	4.20	5.377
17	H	CF_3	H	2.30	5.638
18	H	H	CF_3	0.80	6.097
19	Me	H	CF_3	0.62	6.208
Chloroquine	-	-	-	14.00	4.854

under the same experimental conditions and possesses the minimum variance in the observed responses [18]. Once a suitable dataset has been selected, the main step of modeling requires molecular/physicochemical properties, followed by variable selection, model generation from different algorithms and validation process using internal and external dataset [19-21].

The current work aimed to obtain a QSAR model of *N*-(1-benzyl-3,5-dimethyl-1*H*-pyrazole-4-yl) benzamide derivatives in order to predict biological activity against human pancreatic ductal adenocarcinoma cell MIA PaCa-2, validate the predictive ability of the developed model through validation methods, calculate the statistical parameter to prove quality of model, and use the obtained model to predict the biological activity against human pancreatic ductal adenocarcinoma cell MIA PaCa-2 on a set of designed compounds (**1**-**15**). And conducting docking studies for all designed compounds (**1**-**15**) and selected protein 6s6a.

2. Experimental

2.1. QSAR studies

2.1.1. Data set

A data set comprised of nineteen *N*-(1-benzyl-3,5-dimethyl-1*H*-pyrazole-4-yl) benzamide derivatives was used in the present study. All compounds and associated data were obtained from literature [22]. The biological activity data were reported as (EC_{50}) values half maximal effective concentration in MIA PaCa-2a pancreatic cancer line. The (EC_{50}) values were converted into (pEC_{50}) using the formula: pEC_{50} = -log EC_{50}, values along with the *N*-(1-benzyl-3,5-dimethyl-1*H*-pyrazole-4-yl) benzamide derivatives structures can be found on Table 1.

Chemical structures of the compounds were done using the ACD/ChemSketch v14.01 software (ACD, Copyright 1994-2013 Advanced Chemistry Development, Inc.), molecular modeling was performed using the Molecular Operating Environment software package (MOE, v2009.10; Chemical Computing Group Inc.). The QSAR model was derived from nineteen molecules which were randomly divided into training set of fifteen molecules and test set of four molecules was used to validate QSAR model.

2.1.2. Molecular descriptors generation

Different molecular descriptors (physicochemical properties) [23] were calculated for each molecule after the low energy conformer of structures were generated, these descriptors included electronic, spatial, and structural descriptor were calculated using MOE and ACD lab programs. In order to select the best subset of descriptors, and avoid difficulties in forming QSAR models, hence the predictivity and the generalization of the model fail under these conditions, highly correlated descriptors were excluded using correlation matrix, the nine descriptors used to generate QSAR model denoted as molecular weight (MW), molar volume (MV), molar refractivity (Mr), sum of atomic polarizabilities (S-aPol), total polar surface area (T-pSA), density (D), index of refraction (InR), surface tension (ST), and Log octanol/water partition coefficient (log P(o/w)) reported in Table 2.

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

Compound	MW	MV	Mr	S-aPol	T-pSA	D	lnR	ST	Log P(o/w)
1	411.5050	359.0000	12.4145	67.3338	55.9685	0.9795	1.6070	43.5000	4.8820
3	454.5300	369.0000	13.2528	71.6626	143.1298	1.0129	1.6310	48.5000	3.8230
4	468.5570	392.1000	13.7479	74.7562	135.8367	1.0049	1.6160	45.3000	4.2180
5	482.5840	413.3000	14.1937	77.8498	122.8609	0.9937	1.6050	43.7000	4.4150
6	482.5840	408.1000	14.2149	77.8498	110.3188	0.9958	1.6100	44.8000	4.5590
7	496.6110	423.3000	14.6494	80.9434	94.9803	0.9829	1.6060	43.5000	5.0210
9	474.6050	392.1000	13.8371	78.7570	137.5979	0.9870	1.6160	45.3000	4.5430
10	482.5840	407.3000	14.1945	77.8498	138.3996	0.9899	1.6110	43.9000	4.5530
11	498.5830	413.7000	14.3987	78.6518	168.2368	1.0106	1.6060	44.3000	3.9237
13	498.5830	413.7000	14.3950	78.6518	174.5284	1.0126	1.6060	44.3000	4.1740
14	503.0020	401.3000	14.2636	76.2694	138.1049	1.0457	1.6230	46.1000	4.8080
15	503.0020	401.3000	14.2598	76.2694	135.7901	1.0411	1.6230	46.1000	4.8470
16	503.0020	401.3000	14.2598	76.2694	136.9149	1.0436	1.6230	46.1000	4.8100
18	536.5540	422.0000	14.3648	77.5204	234.1733	1.0925	1.5860	41.5000	5.1528
19	550.5810	437.2000	14.8190	80.6140	235.1974	1.0725	1.5830	40.4000	5.4858

Table 3. Comparison of squared correlation coefficients of the models.

Models	r^2
Model 1	0.852
Model 2	0.835
Model 3	0.937
Model 4	0.853
Model 5	0.896

Table 4. Statistical parameters used for statistical quality of model.

r	r^2	Q^2	s	F	RMSE	*P* value
0.968	0.937	0.880	0.117	192.638	0.109	0.000

Table 5. Experimental and predicted pEC_{50} for training set and cross validation against human pancreatic cancer cell line (MIA PaCa-2).

Compound	$pEC_{50\ exp.}$	$pEC_{50\ pred.}$	Residuals	$CV_{\ pred.}$	Residuals
1	5.0000	5.1001	-0.1001	5.1383	-0.1383
3	4.3770	4.5695	-0.1925	4.7145	-0.3375
4	5.2080	4.9679	0.2401	4.9343	0.2737
5	5.1940	5.1165	0.0775	5.1021	0.0919
6	4.9590	5.0095	-0.0505	5.0151	-0.0561
7	5.0510	5.1412	-0.0902	5.1837	-0.1327
9	4.8540	4.8826	-0.0286	4.8875	-0.0335
10	5.2080	5.0816	0.1264	5.0616	0.1464
11	5.0710	5.0972	-0.0262	5.1141	-0.0431
13	5.0970	5.1425	-0.0455	5.1541	-0.0571
14	5.2010	5.2244	-0.0234	5.2324	-0.0314
15	5.2290	5.1971	0.0319	5.1860	0.0430
16	5.3770	5.2095	0.1675	5.1538	0.2232
18	6.0970	6.1753	-0.0783	6.2502	-0.1532
19	6.2080	6.2160	-0.0080	6.2228	-0.0148

$$pEC_{50} = 1.63148 + 0.60842 \times \log P(o/w) - 0.01141 \times InR + 0.00547 \times T\text{-}pSA \quad (1)$$

$$pEC_{50} = -5.14822 + 0.39163 \times \log P(o/w) + 0.00728 \times MV + 5.51570 \times D \quad (2)$$

$$pEC_{50} = 3.16492 + 0.12375 \times \log P(o/w) + 6.97797 \times D - 0.12652 \times ST \quad (3)$$

$$pEC_{50} = 1.85725 + 0.61188 \times \log P(o/w) + 0.00560 \times T\text{-}pSA - 0.00363 \times S\text{-}aPol \quad (4)$$

$$pEC_{50} = 5.53650 + 0.44173 \times \log P(o/w) - 0.06791 \times ST + 0.00455 \times T\text{-}pSA \quad (5)$$

2.1.3. QSAR model development

The QSAR model were developed from the training set compounds where the independent variables molecular descriptors and dependent response variable (pEC_{50}) were subjected to multiple linear regressions (MLR) analysis, several QSAR models were developed. The comparison of squared correlation coefficients of the models reported in Table 3.

The resulting QSAR model Equation (3) exhibited a high regression coefficient. The model was justified by statistical parameters such as the correlation coefficient (*r*), squared correlation coefficient (r^2), cross-validated regression coefficient (Q^2), standard error of estimate (s), F-test value (F), and the root mean squared error (RMSE), and validated using random test set compounds Table 4, and was evaluated for the robustness of its predictions via the cross-validation coefficient.

2.1.4. Validation of QSAR model

The developed model was validated internally by training set compounds using leave-one-out (LOO) cross-validation technique. In this technique, one compound is eliminated from the data set at random in each cycle and the model is built using the rest of the compounds. The model thus formed is used for predicting the activity of the eliminated compound. The process is repeated until all the compounds are eliminated once. The cross-validated regression coefficient (Q^2) was calculated.

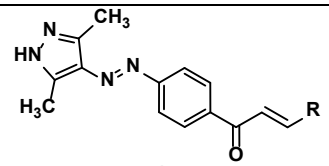
External validation was performed in order to determine the predictive capacity of the developed model as judged by its application for the prediction of test set activity values.

The observed activities and those calculated by QSAR model (Equation 3) for training set and test set were presented in Table 5 and 6.

Table 6. Predicted pEC_{50} values of test set

Compound	$pEC_{50\ exp.}$	$pEC_{50\ pred.}$	Residuals
2	5.0360	4.5665	0.4695
8	5.1940	4.9549	0.2391
12	5.2080	5.1417	0.0663
17	5.6380	6.1317	-0.4937

Table 7. Structures and predicted pEC_{50} values for designed 3,5-dimethyl-4-substituted-pyrazole derivatives against human pancreatic cancer cell line (MIA PaCa-2).



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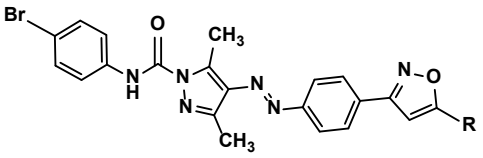

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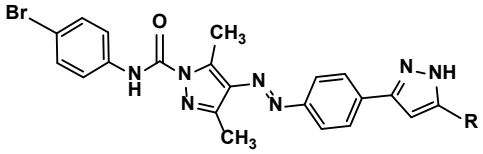


11-15

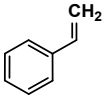
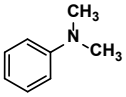
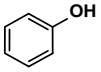
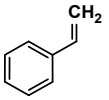
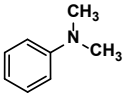
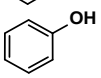
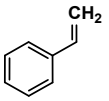
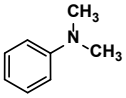
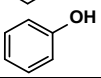
Compound	R	$pEC_{50pred.}$
1		5.1410
2		4.9845
3		6.0610
4		5.3002
5		4.8785
6		5.2189
7		4.9615
8		5.4439
9		5.4630
10		4.9848
11		5.0520
12		4.8002
13		5.2539
14		5.2989
15		4.7922

Table 8. Binding scores and interactions of the docked designed 3,5-dimethyl-4-substituted-pyrazole derivatives (**1**-**15**) on the active site of 6s6a.

Compound	S (kcal/mol)	Amino acid interaction	Type of interaction	Length (Å)
1	-24.8616	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-
		ThrA21	Metal complexation (Mg)	2.16
		ThrA42	Metal complexation (Mg)	2.22
2	-22.0658	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-
		ThrA21	Metal complexation (Mg)	2.16
		ThrA42	Metal complexation (Mg)	2.22
3	-20.1774	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-
4	-24.8373	ArgA37	π-cation interaction	-
		ThrA21	Metal complexation (Mg)	2.16
		ThrA42	Metal complexation (Mg)	2.22
5	-18.9748	ArgA37	π-cation interaction	-
		AspA130	Hydrogen bond	2.03
6	-22.5543	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-
7	-18.0398	ArgA37	π-cation interaction	-
		ArgA37	Hydrogen bond	3.04
8	-19.4697	ArgA37	π-cation interaction	-
		ArgA37	π -cation interaction	-
		LysA128	π-cation interaction	-
9	-20.3244	ArgA37	π-cation interaction	-
10	-22.4642	LysC179	π-cation interaction	-
		SerC76	Hydrogen bond	3.04
11	-21.7914	ArgA37	π-cation interaction	-
		ArgA37	Hydrogen bond	2.97
		LysA128	π-cation interaction	-
12	-21.0138	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-
13	-24.0026	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-
14	-22.5484	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-
15	-18.7338	ArgA37	π-cation interaction	-
		LysA128	π-cation interaction	-

2.1.5. Predict the activity of designed 3,5-dimethyl-4-substituted-pyrazole derivatives

Chemical structures of the designed 3,5-dimethyl-4-substituted-pyrazole derivatives (**1**-**15**) were done using the ACD/ChemSketch, the developed QSAR model (Equation (3)) was used to predict their activity against human pancreatic ductal adenocarcinoma cell line MIA PaCa-2. The predicted activity expressed as pEC_{50} along with the structures reported in Table 7.

2.2. Molecular docking

Docking is a molecular modelling technique that is used to predict how a protein interacts with small molecules (ligands) by predicting of the most possible type of interaction, the binding affinities, and the orientations of the docked ligands at the active site of the target protein. Molecular docking study was carried out in order to elucidate which of the designed 3,5-dimethyl-4-substituted-pyrazole derivatives (**1**-**15**) has the best binding affinity against the mechanistic (or mammalian) target of rapamycin complex 1 (mTORC1). The structure of mTORC1 used in the study was obtained from Protein Data Bank with PDB code 6s6a, structures of the designed 3,5-dimethyl-4-substituted-pyrazole derivatives (**1**-**15**) were prepared and saved as mol files, the prepared compounds were docked with prepared structure of 6s6a protein using MOE program. The binding score (S) of the complexes and amino acid interactions are reported in Table 8.

3. Results and discussion

3.1. QSAR studies

The studied compounds which were an autophagy modulator showed a promising role as anticancer agents. In the present work, structure activity relationship model was developed that could correlate the structural features with biological activity.

The developed model showed squared correlation coefficient (r^2 = 0.937) which indicates the correlation between the activity (dependent variable) the molecular descriptors (independent variable) for the training set data, and squared cross-validation (Q^2 = 0.880) which indicates that the newly developed QSAR model has a good prediction. Three molecular descriptors denoted as log octanol/water partition coefficient (log P(o/w)), density (D), and surface tension (ST) were significantly correlated with anticancer activity. It is evident from the Equation (3) that among the molecular descriptors, log P(o/w) and D are positively correlated, that mean the biological activity increases when the values of these descriptors are positively increased. On the other hand, the descriptor ST negatively correlated with anticancer activity, that mean the biological activity decreases when the value of this descriptor is increase. Four compounds denoted by (test set) were used as external validation for developed QSAR model, and it was found that the predicted values through the QSAR model show compliance with their experimental values and r^2 = 0.990, all statistical parameters calculated to evaluate the quality of the QSAR model were in suitable range. Figure 1 shows the correlation plots of the experimental versus predicted pEC_{50} values for training set, cross-validation and test set compounds against pancreatic cancer cell line.

3.2. Docking study

Molecular docking study was carried out between the target (mTORC1) and designed 3,5-dimethyl-4-substituted-pyrazole derivatives (**1**-**15**). All compounds were found to inhibit the receptor by occupying the active sites of the target (mTORC1). The binding affinity values for designed compounds range from -24.8616 to -18.0398 kcal/mol as reported in Table 8.

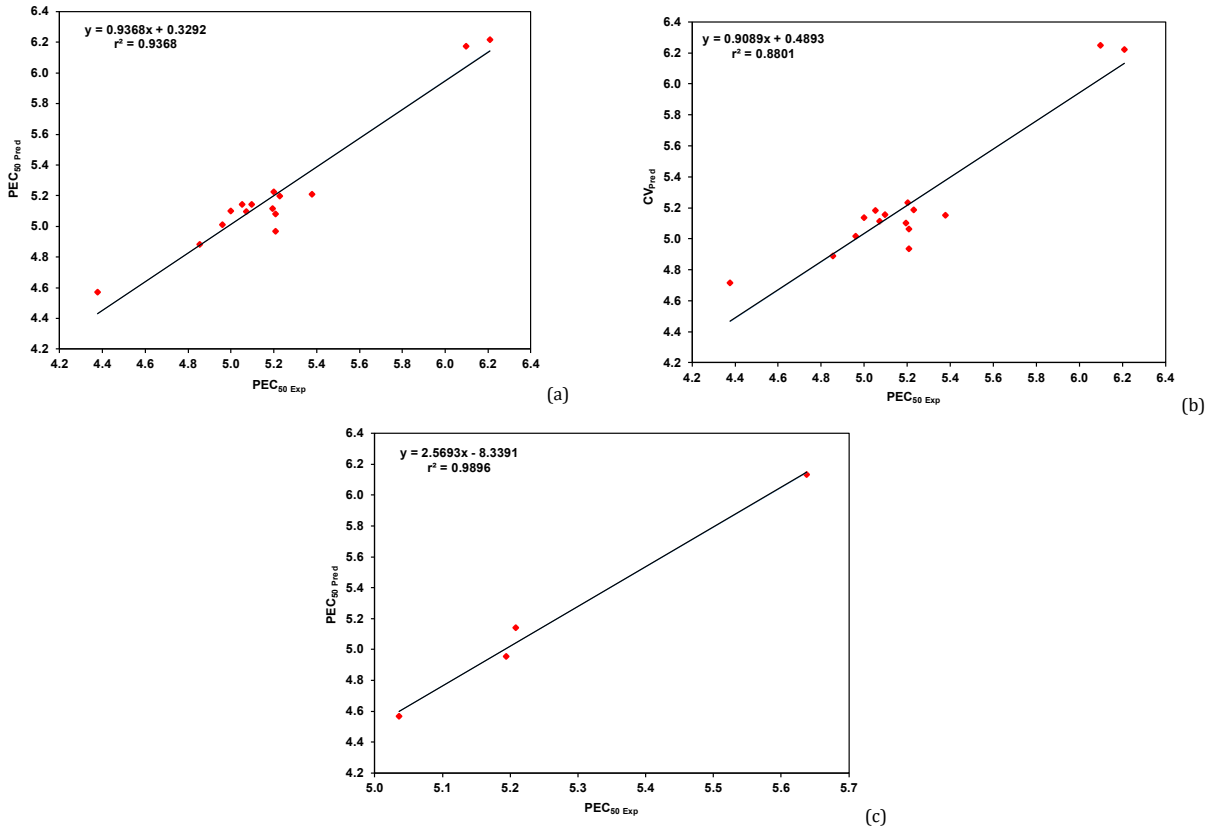
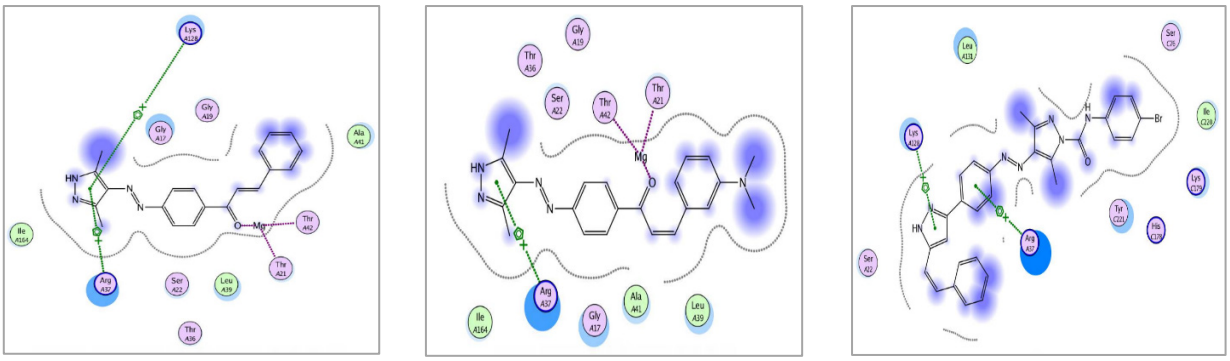
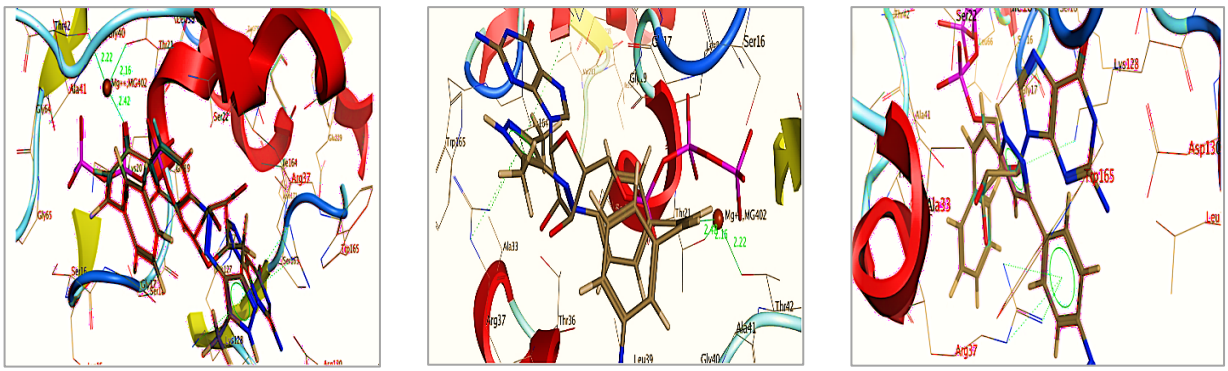


Figure 1. Predicted versus experimental pEC_{50} values of (a) training set, (b) cross validation set, and (c) test set against human pancreatic cancer MIA PaCa-2.



Compound **1** Compound **4** Compound **13**

Figure 2. 2D molecular docking model of compounds **1**, **4** and **13** with 6s6a.



Compound **1** Compound **4** Compound **13**

Figure 3. 3D model of the interaction between compounds **1**, **4** and **13** with 6s6a.

However, three ligands (**1**, **4**, and **13**) have higher binding score, which ranges from -24.8616 to -24.0026 kcal/mol, ligand **1** formed two π-cation interaction with ArgA37 and LysA128, and two metal complexations with Mg ion with ThrA21 and ThrA42. Ligand **4** formed three interactions, a π-cation interaction with ArgA37 and two metal complexations with Mg ion with ThrA21 and ThrA42. Ligand **13** formed two π-cation interactions with ArgA37 and LysA128 (Figure 2 and 3).

4. Conclusion

In this work, a QSAR study was performed based on theoretical molecular descriptors, the built model serves as a guide for providing the structural requirements affecting the anticancer activity against pancreatic cancer cell line MIA PaCa-2, through the identification of the most relevant selected molecular descriptors in the models, comprehensive assessment (internal and external validation) indicate that the built QSAR model was robust and satisfactory, and that the selected descriptors could account for the structural features responsible for anticancer drugs activity of the compounds. The QSAR model developed and molecular docking in this study can provide a useful tool to predict the activity of new compounds and also to design new compounds with high activity.

Disclosure statement

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