European Journal of Chemistry

View Journal Online
View Article Online

QSAR and docking studies of pyrazole analogs as antiproliferative against human colorectal adenocarcinoma cell line HT-29

Hiba Hashim Mahgoub Mohamed [1,2,*], Amna Bint Wahab Elrashid Mohammed Hussien [3] and Ahmed Elsadig Mohammed Saeed [1]

[1] *Department of Chemistry, College of Science, Sudan University of Science and Technology, Khartoum, 2288, Sudan*
[2] *Department of Chemistry, Ibn Sina University, Khartoum, 10995, Sudan*
[3] *College of Animal Production Science and Technology, Sudan University of Science and Technology, Khartoum, 2288, Sudan*

* *Corresponding author at: Department of Chemistry, College of Science, Sudan University of Science and Technology, Khartoum, 2288, Sudan.*
e-mail: hibahashim.m@hotmail.com (H.H.M. Mohamed).

RESEARCH ARTICLE

10.5155/eurjchem.13.3.319-326.2259

Received: 10 March 2022
Received in revised form: 21 April 2022
Accepted: 01 July 2022
Published online: 30 September 2022
Printed: 30 September 2022

KEYWORDS

QSAR
HT-29
Pyrazole
Molecular modeling
Antiproliferative activity
Colorectal adenocarcinoma

ABSTRACT

In-silico quantitative structure-activity relationship (QSAR) study was performed to develop a model on a series of novel pyrazole derivatives containing acetamide moiety which exhibited considerable antiproliferative activity against human colorectal adenocarcinoma cell line HT-29. The model obtained has a correlation coefficient (r) of 0.9693, squared correlation coefficient (r^2) of 0.9395 and a leave-one-out (LOO) cross-validation coefficient (Q^2) value of 0.8744. The predictive power of the developed model was confirmed by the external validation which has an r^2 value of 0.9488. These parameters confirm the stability and robustness of the model to predict the activity of a new designed set of 3,5-dimethyl-pyrazole derivatives (22-36), results indicated that the compounds 26, 31, 35, and 36 showed the strongest antiproliferative activity with (IC_{50} = 0.182, 0.172, 0.166 and 0.024 µM, respectively) against human colorectal adenocarcinoma cell line HT-29 compared to the reference vemurafenib with (IC_{50} = 1.52 µM). Molecular docking was performed on the new designed compounds with the human colorectal adenocarcinoma cell line 5JRQ protein. The docking results showed that compounds 26, 31, 35, and 36 have docking affinity of -8.528, -5.932, 23.017 and 18.432 kcal/mol, respectively.

Cite this: *Eur. J. Chem.* **2022**, *13(3)*, 319-326 **Journal website**: www.eurjchem.com

1. Introduction

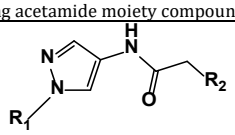
Colorectal cancer (CRC) is the term that refers to colon cancer (CC) and rectal cancer (RC), which is considered as a single tumor entity [1], is the third most common malignancy and the second in mortality [2]. The reasons for these increases are complex, but genetic and environmental factors play an important role [3-5]. CRC is caused by uncontrolled cell proliferation and division, which occurs when genetic [6], metabolic [7], and carcinogenic factors [8] damage the DNA and inducing mutations [9,10]. This process involves the activation of oncogenes and/or the deactivation of a tumor suppressor gene, leading to uncontrolled cell cycle progression and inactivation of apoptosis. The standard treatment for CRC is chemotherapy, surgery and radiation or a combination of these for advanced stage disease, this approach depends on tumor characteristics, such as location, size, extent of cancer metastasis and the health status of the patient [11]. However, these treatment options have had limited impact as cancer progress which make the development of new anticancer drugs an emergency need.

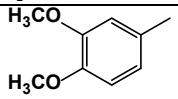
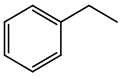
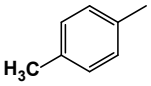
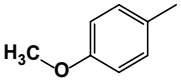
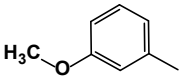
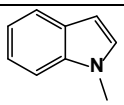
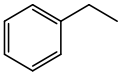
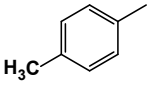
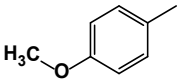
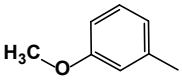
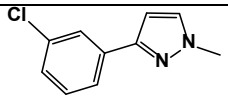
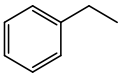
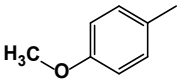
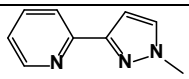
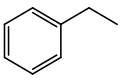
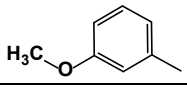
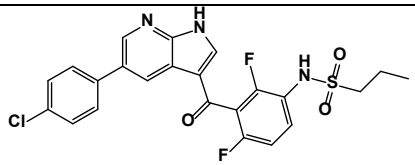
Pyrazole is an unsaturated five-membered ring containing two nitrogen atoms at positions 1 and 2 and, among heterocyclic compounds, represents one of the most important chemical scaffolds in medicinal chemistry [12], it is displaying a broad spectrum of pharmaceutical and biological activity such as anti-cancer, anti-inflammatory, anti-fungal, anti-bacterial, anti-insecticidal, analgesic, anticonvulsant, anti-diabetic, anti-pyretic, anti-arrhythmic, anti-depressant, anti-hyperglycemic, anti-oxidant, and herbicidal *etc.* [13-15].

Quantitative structure-activity relationships have been applied for decades in the development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable statistical model for prediction of the activities of new chemical entities and improve the inhibitory of drugs. The fundamental principle underlying the formalism is that the difference in structural properties is responsible for the variations in biological activities of the compounds [16], QSAR modeling involves main steps: (*i*) Model building by collecting the data set compounds, (*ii*) Model validation with internal validation using training set compounds to assess its quality, and (*iii*) Model validation with

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
https://dx.doi.org/10.5155/eurjchem.13.3.319-326.2259

Table 1. Biological activities and structures of pyrazole containing acetamide moiety compounds obtained from literature [19].



Compound	R_1	R_2	IC_{50} (μM)	pIC_{50}
1	$-CH_3$		32.80	4.48
2	$-CH_2CH_3$		25.62	4.59
3			8.43	5.07
4			11.54	4.94
5			8.73	5.06
6			9.33	5.03
7			7.98	5.10
8	$-CH_2CH_3$		49.87	4.30
9			12.35	4.91
10			26.55	4.58
11			24.14	4.62
12			12.74	4.89
13			10.13	4.99
14	$-CH_3$		22.56	4.65
15	$-CH_2CH_3$		12.92	4.89
16			5.70	5.24
17			2.17	5.66
18	$-CH_3$		25.36	4.60
19	$-CH_2CH_3$		26.79	4.57
20			12.65	4.90
21			6.16	5.21
Vemurafenib			1.52	5.82

an external validation using test set compounds to assess its predictability [17,18].

The current study aimed to obtain a QSAR model of a series of novel pyrazole derivatives containing acetamide moiety in order to predict antiproliferative activity against human colorectal adenocarcinoma cell line HT-29, 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 antiproliferative activity against human colorectal adenocarcinoma cell line HT-29, on a set of designed compounds (**22-36**) and conducting docking studies for the designed compounds on the active site of selected protein 5JRQ.

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

Compound	Dipole moment, D	E_{Total}, kcal/mol	E, kcal/mol	E_{tor}, kcal/mol	a-acc	a-don	MW, g/mol	HVSA	Log P(o/w)
1	1.515	-83153.773	57.982	2.660	4.000	1.000	275.308	264.303	0.621
2	1.282	-86747.898	55.685	-0.516	4.000	1.000	289.335	281.535	0.962
3	1.646	-102128.05	82.666	3.463	4.000	1.000	351.406	334.802	2.409
4	1.981	-98533.953	84.380	2.105	4.000	1.000	337.379	317.569	2.275
5	1.556	-102129.97	84.620	3.244	4.000	1.000	351.406	334.802	2.573
7	1.175	-109505.21	91.910	1.518	5.000	1.000	367.405	347.301	2.268
8	1.373	-75766.867	28.839	-0.913	2.000	1.000	268.320	254.273	1.762
9	0.575	-91148.398	55.477	3.107	2.000	1.000	330.391	307.539	3.209
10	1.082	-87554.789	55.431	2.594	2.000	1.000	316.364	290.307	3.075
11	1.803	-98528.367	65.436	2.663	3.000	1.000	346.390	320.039	3.031
13	1.081	-98526.953	62.793	2.650	3.000	1.000	346.390	320.039	3.068
14	3.334	-88489.617	35.376	1.618	3.000	1.000	315.764	280.564	1.189
15	3.278	-92083.945	33.123	-1.529	3.000	1.000	329.791	297.796	1.530
16	3.725	-107464.77	59.373	2.556	3.000	1.000	391.862	351.062	2.977
17	2.671	-81687.093	39.118	2.625	4.000	1.000	282.307	255.444	-0.516
19	2.693	-85274.539	44.899	-0.677	4.000	1.000	296.334	272.676	-0.175
20	3.306	-100656.38	71.281	3.465	4.000	1.000	358.405	325.942	1.273
21	2.047	-108038.72	76.969	3.103	5.000	1.000	374.404	338.442	1.132

* Total energy (E_{Total}), potential energy (E), torsion energy (E_{Tor}), number of H-bond acceptor atoms (a-acc), number of H-bond donor atoms (a-don), molecular weight (MW), total hydrophobic VdW surface area (HVSA), and log octanol/water partition coefficient Log P(o/w).

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

r	r^2	Q^2	s	F	RMSE	p-value
0.9693	0.9395	0.8744	0.0680	248.592	0.0640	0.0000

2. Experimental

2.1. QSAR studies

2.1.1. Data set

A set comprised of 21 derivatives of pyrazole containing acetamide moiety which showed antiproliferative activity against human colorectal adenocarcinoma cell line HT-29 reported by Wang *et al.* [19] was used in the present study, and their antiproliferative activities were expressed as IC_{50} values half maximal inhibitory concentration. The IC_{50} (μM) values were converted into IC_{50} (M)and then to pIC_{50} values using the formula pIC_{50} = - log [IC_{50}]. The structures and pIC_{50} values of the derivatives of pyrazole containing the acetamide moiety are listed in Table 1.

The chemical structures of the compounds done made using the ACD/ChemSketch v.14.01 software (Copyright 1994-2013, Advanced Chemistry Development, Inc.) [20]. Molecular modeling was performed using the Molecular Operating Environment software package (MOE, v2009.10; Chemical Computing Group Inc.) [21]. The data set was randomly divided into a training set that comprises 80% of the dataset that was used to build the QSAR model, while the remaining 20% of the dataset test set was used to validate the QSAR model (18 and 3 molecules, respectively).

2.1.2. Molecular descriptor generation

Molecular descriptors were calculated for each molecule after they were subjected to energy minimization, and these descriptors include 3D descriptors (e.g., dipole moment, total energy, potential energy, and torsion energy) and 2D descriptors (e.g., number of H-bond acceptor atoms, number of H-bond donor atoms, molecular weight, total hydrophobic van der Waals (VdW) surface area, and log octanol/water partition coefficient). These descriptors were calculated using MOE programs. In order to select the best subset of descriptors, highly correlated descriptors were excluded using correlation matrix then ratio of molecules to the descriptors used is 5:1. The nine descriptors used to generate the QSAR model are denoted as dipole moment, total energy (E_{Total}), potential energy (E), torsion energy (E_{Tor}), number of H-bond acceptor atoms (a-acc), number of H-bond donor atoms (a-don), molecular weight (MW), total hydrophobic VdW surface area (HVSA) and log octanol/water partition coefficient Log P(o/w) and are listed in Table 2.

2.1.3. QSAR model development

The correlation of the calculated descriptors with each other was calculated and collinear descriptors were specified, those with higher correlation towards activity were retained and the others were eliminated. Subsequently, multiple linear regression (MLR) analysis were performed on the training set. Where calculated molecular descriptors served as an independent variable and observed inhibition (pIC_{50}) values were used as a dependent variable. Several QSAR models were developed and the resulting QSAR model Equation (1) showed a high regression coefficient. The values of the regression coefficient and statistical parameters are listed in Table 3.

$$pIC_{50} = 1.94587 - 0.00342 \times E + 0.01671 \times E_{Tor} + 0.01030 \times HVSA - 0.04588 \times \log P(o/w) \quad (1)$$

2.1.4. Validation of the QSAR model

To evaluate the robustness of the model, internal validation of the training set was performed using the 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 cross-validated regression coefficient (Q^2) values were thereafter calculated according to Equation (1). External validation was performed to determine the predictive capacity of the developed model by its application to predict the values of the test set. The observed activities and those calculated by QSAR model (Equation (1)) for the training set and test set were presented in Tables 4 and 5.

2.1.5. Predict the activity of designed 3,5-dimethylpyrazole derivatives (22-36)

The chemical structures of the 3,5-dimethylpyrazole derivatives designed (**22**-**36**) were carried out using the ACD/ChemSketch, the QSAR model developed (Equation (1)) was used to predict their activity against the human colorectal adenocarcinoma cell line (HT-29). The predicted activity expressed as pIC_{50} along with the structures reported in Table 6.

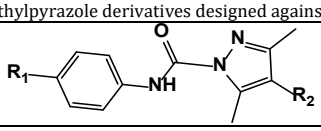
Table 4. Experimental and predicted pIC_{50} for training set and cross-validation against human colorectal adenocarcinoma cell line (HT-29).

Compound	$pIC_{50exp.}$	$pIC_{50pred.}$	Residuals	$CV_{pred.}$	Residuals
1	4.480	4.486	-0.006	4.489	-0.009
2	4.590	4.602	-0.012	4.607	-0.017
3	5.070	5.059	0.011	5.057	0.013
4	4.940	4.859	0.081	4.831	0.109
5	5.060	5.041	0.019	5.038	0.023
7	5.100	5.130	-0.030	5.146	-0.046
8	4.300	4.370	-0.070	4.411	-0.111
9	4.910	4.828	0.082	4.803	0.107
10	4.580	4.649	-0.069	4.676	-0.096
11	4.890	4.924	-0.034	4.929	-0.039
13	4.990	4.931	0.060	4.921	0.069
14	4.650	4.687	-0.037	4.697	-0.047
15	4.890	4.804	0.086	4.732	0.158
16	5.240	5.265	-0.025	5.282	-0.042
17	4.600	4.511	0.090	4.428	0.173
19	4.570	4.598	-0.028	4.610	-0.040
20	4.900	5.059	-0.159	5.100	-0.200
21	5.210	5.168	0.042	5.152	0.058

Table 5. Predicted pIC_{50} values of the test set.

Compound	$pIC_{50exp.}$	$pIC_{50pred.}$	Residuals
6	5.030	5.132	-0.102
12	4.620	4.803	-0.183
18	5.660	5.358	0.302

Table 6. Structures and predicted pIC_{50} values for 3,5-dimethylpyrazole derivatives designed against human colorectal adenocarcinoma cell line (HT-29).



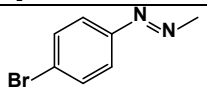
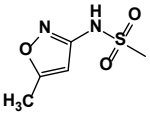
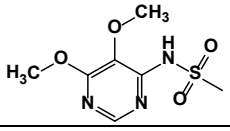
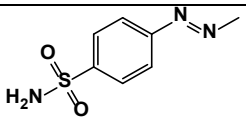
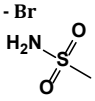
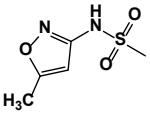
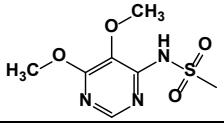
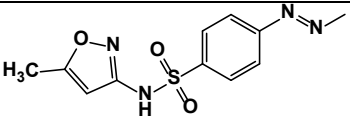
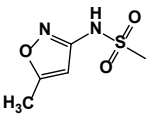
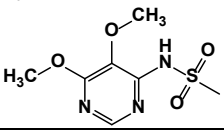
Compound	R_1	R_2	$pIC_{50pred.}$
22	-		4.970
23	- Br		5.237
24			5.156
25			6.000
26			6.739
27	-		4.890
28	- Br		5.152
29			5.061
30			5.933
31			6.764
32	-		5.745
33	- Br		6.003
34			5.916
35			6.780
36			7.627

Table 7. Binding scores and interactions of the designed 3,5-dimethyl-pyrazole derivatives (**22-36**) docked on the active site of (5JRQ).

Compound	S (kcal/mol)	Amino acid interaction	Type of interaction
22	-6.087	Phe583	Arene - Arene interaction
23	-9.438	No interaction	-
24	-9.175	Thr529	Hydrogen bond
		Phe583	Arene - Arene interaction
25	-9.924	Phe583	Arene - Arene interaction
26	-8.528	Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
27	-2.714	Gly596	Hydrogen bond
		Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
28	-3.594	Gly596	Hydrogen bond
		Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
29	-4.358	Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
30	-6.082	Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
31	-5.932	Lys483	Arene - Arene interaction
		Phe583	Arene - Arene interaction
32	7.929	Lys483	Hydrogen bond
		Phe583	Arene - Arene interaction
33	11.112	Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
34	11.500	Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
35	23.017	Asp594	Hydrogen bond
		Lys483	Arene - Cation interaction
		Lys483	Arene - Cation interaction
		Phe583	Arene - Arene interaction
36	18.432	Thr529	Hydrogen bond
		Asp594	Arene - Cation interaction
		Lys483	Arene - Cation interaction

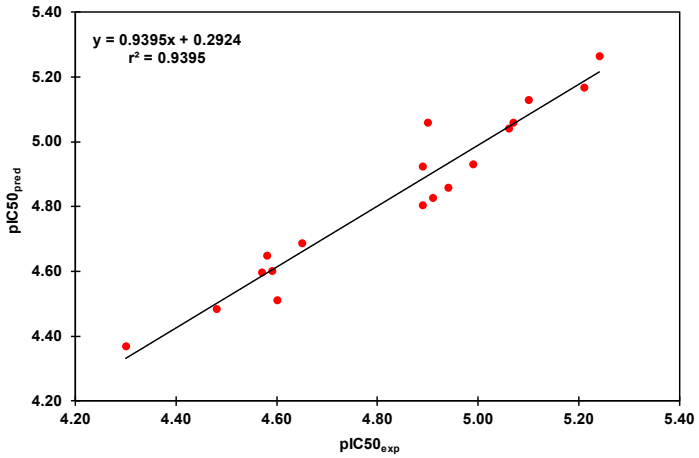


Figure 1. Predicted versus experimental pIC_{50} values of training set against human colorectal adenocarcinoma cell line (HT-29).

2.2. Molecular docking

The docking simulation was carried out using the MOE program [21]. For this purpose, the structure of protein was obtained from Protein Data Bank with PDB code (5JRQ) [22], structures of the new designed 3,5-dimethylpyrazole derivatives (**22-36**) were build using ACD/ChemSketch v.14.01 software [20] then saved as mol file, then docking simulation was performed. The binding score (S) of the complexes and amino acid interactions are listed in Table 7.

3. Results and discussion

3.1. QSAR studies

In the present work, the structure-activity relationship model was developed to correlate the structural characteristics with the biological response of the compounds studied that had antiproliferative activity against the human colorectal adenocarcinoma cell line HT-29. The developed model showed a squared correlation coefficient ($r^2 = 0.9395$) which indicates the correlation between the activity (dependent variable) the molecular descriptors (independent variable) for the training set data, and squared cross-validation ($Q^2 = 0.8744$) which indicates that the newly developed QSAR model has a good prediction.

Four molecular descriptors denoted as potential energy (E), torsion energy (E_{Tor}), total hydrophobic VdW surface area and log octanol/water partition coefficient Log P(o/w) were significantly correlated with antiproliferative activity against the human colorectal adenocarcinoma cell line HT-29. Equation (1) shows that among the molecular descriptors, E_{Tor} and HVSA are positively correlated, which means that biological activity increases when the values of these descriptors are positively increased. On the other hand, the descriptor E and Log P(o/w) are negatively correlated with antiproliferative activity, that mean the biological activity decreases when the value of this descriptor is increase.

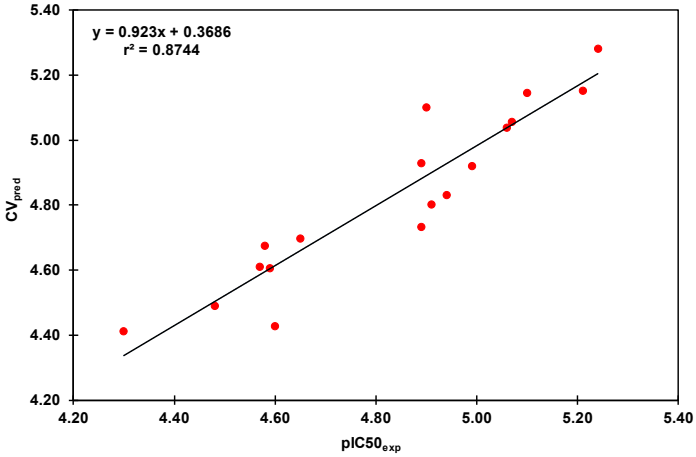


Figure 2. Predicted versus experimental pIC_{50} values of cross validation against human colorectal adenocarcinoma cell line (HT-29).

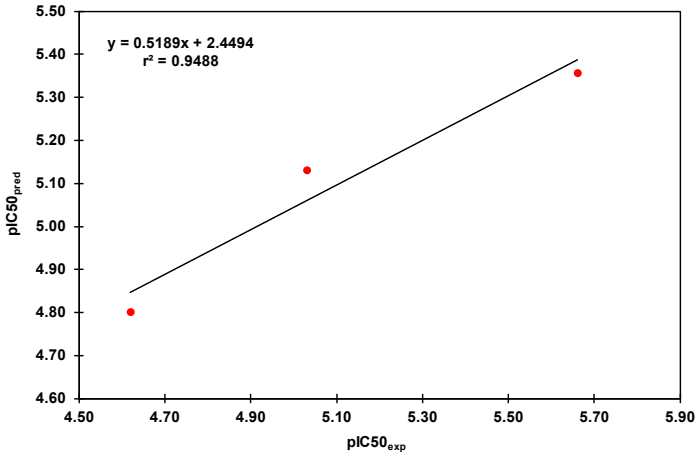
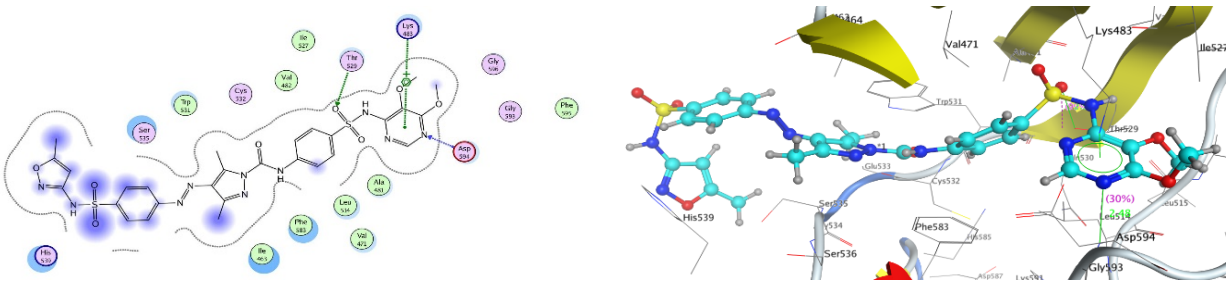


Figure 3. Predicted versus experimental pIC_{50} values of the test set against the human colorectal adenocarcinoma cell line (HT-29).



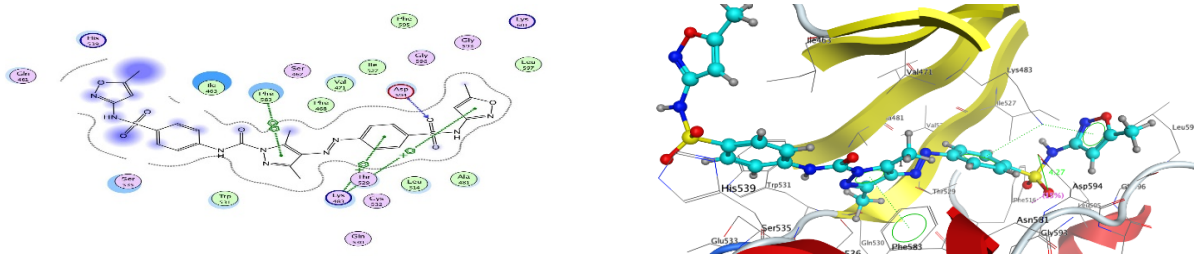
(a) (b)

Figure 4. (a) 2D molecular docking model of compound **36** with 5JRQ and (b) 3D model of the interaction between compound **36** and the binding site of 5JRQ.

Test set compress of three compounds which 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 = 0.9488), all statistical parameters calculated to evaluate the quality of the QSAR model were in suitable range. Figures 1-3 show the correlation graphs of the experimental versus predicted pIC_{50} values for the training set, cross-validation, and test set compounds against the human colorectal adenocarcinoma cell line (HT-29), respectively.

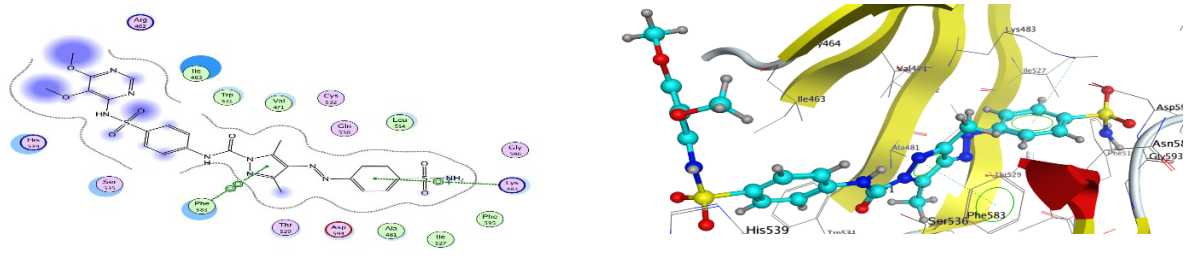
3.2. Docking study

A molecular docking study was performed between the target (5JRQ) and designed 3,5-dimethylpyrazole derivatives (**22-36**). All compounds were found to inhibit the receptor by occupying the active sites of the target (5JRQ). The binding affinity values for designed compounds range from to -9.438 to 23.017 kcal/mol as reported in Table 7 (Figures 4-6).



(a) (b)

Figure 5. (a) 2D molecular docking model of compound **35** with 5JRQ and (b) 3D model of the interaction between compound **35** and the binding site of 5JRQ.



(a) (b)

Figure 6. (a) 2D molecular docking model of compound **31** with 5JRQ and (b) 3D model of the interaction between compound **31** and the binding site of 5JRQ.

4. Conclusions

The developed QSAR model presents a satisfactory correlation with inhibition activity against the human colorectal adenocarcinoma cell line HT-29, and met the criteria for the minimum recommended value of validation parameters for a generally acceptable QSAR model, and molecular docking analysis has shown that all new compounds have good inhibitor activity. The generated QSAR model provides a valuable approach for ligand-base design, while molecular docking studies provide a valuable approach for structure-base design. These two approaches will be of great help to pharmaceutical and medicinal chemists in designing and synthesis of a new antiproliferative agent.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Ahmed Elsadig Mohammed Saeed, Hiba Hashim Mahgoub Mohamed; Methodology: Hiba Hashim Mahgoub Mohamed, Ahmed Elsadig Mohammed Saeed; Software: Hiba Hashim Mahgoub Mohamed; Validation: Hiba Hashim Mahgoub Mohamed; Formal Analysis: Hiba Hashim Mahgoub Mohamed; Investigation: Amna Bint Wahab Elrashid Mohammed Hussien, Ahmed Elsadig Mohammed Saeed; Resources: Hiba Hashim Mahgoub Mohamed, Amna Bint Wahab Elrashid Mohammed Hussien; Data Curation: Hiba Hashim Mahgoub Mohamed; Writing - Original Draft: Hiba Hashim Mahgoub Mohamed; Writing - Review and Editing: Hiba Hashim Mahgoub Mohamed, Ahmed Elsadig Mohammed Saeed, Amna Bint Wahab Elrashid Mohammed Hussien.

ORCID and Email

Hiba Hashim Mahgoub Mohamed
hibahashim.m@hotmail.com
https://orcid.org/0000-0002-1294-6130
Amna Bint Wahab Elrashid Mohammed Hussien
amnaelrasheed@gmail.com
https://orcid.org/0000-0001-7588-0231
Ahmed Elsadig Mohammed Saeed
aemsaeed@gmail.com
https://orcid.org/0000-0002-7317-8040

References

[1]. El Bali, M.; Bakkach, J.; Bennani Mechita, M. Colorectal cancer: From genetic landscape to targeted therapy. *J. Oncol.* **2021**, *2021*, 9918116.
[2]. Sawicki, T.; Ruszkowska, M.; Danielewicz, A.; Niedźwiedzka, E.; Arłukowicz, T.; Przybyłowicz, K. E. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. *Cancers (Basel)* **2021**, *13*.
[3]. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R. L.; Torre, L. A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2018**, *68*, 394–424.
[4]. Picard, E.; Verschoor, C. P.; Ma, G. W.; Pawelec, G. Relationships between immune landscapes, genetic subtypes and responses to immunotherapy in colorectal cancer. *Front. Immunol.* **2020**, *11*, 369.
[5]. You, Y. N.; Lee, L. D.; Deschner, B. W.; Shibata, D. Colorectal cancer in the adolescent and young adult population. *JCO Oncol Pract* **2020**, *16*, 19–27.
[6]. Testa, U.; Pelosi, E.; Castelli, G. Colorectal cancer: genetic abnormalities, tumor progression, tumor heterogeneity, clonal evolution and tumor-initiating cells. *Med. Sci. (Basel)* **2018**, *6*.
[7]. Loke, Y. L.; Chew, M. T.; Ngeow, Y. F.; Lim, W. W. D.; Peh, S. C. Colon carcinogenesis: The interplay between diet and gut Microbiota. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 603086.
[8]. Vernia, F.; Longo, S.; Stefanelli, G.; Viscido, A.; Latella, G. Dietary factors modulating colorectal carcinogenesis. *Nutrients* **2021**, *13*, 143.
[9]. Barnes, J. L.; Zubair, M.; John, K.; Poirier, M. C.; Martin, F. L. Carcinogens and DNA damage. *Biochem. Soc. Trans.* **2018**, *46*, 1213–1224.
[10]. Basu, A. K. DNA damage, Mutagenesis and cancer. *Int. J. Mol. Sci.* **2018**, *19*.
[11]. Mármol, I.; Sánchez-de-Diego, C.; Pradilla Dieste, A.; Cerrada, E.; Rodriguez Yoldi, M. J. Colorectal carcinoma: A general overview and future perspectives in colorectal cancer. *Int. J. Mol. Sci.* **2017**, *18*, 197.
[12]. Naim, M. J.; Alam, O.; Nawaz, F.; Alam, M. J.; Alam, P. Current status of pyrazole and its biological activities. *J. Pharm. Bioallied Sci.* **2016**, *8*, 2–17.
[13]. Alsayari, A.; Asiri, Y. I.; Muhsinah, A. B.; Hassan, M. Z. Anticolon cancer properties of pyrazole derivatives acting through xanthine oxidase inhibition. *J. Oncol.* **2021**, *2021*, 5691982.
[14]. Aziz, H.; Zahoor, A. F.; Ahmad, S. Pyrazole bearing molecules as bioactive scaffolds: A review. *J. Chil. Chem. Soc.* **2020**, *65*, 4746–4753.
[15]. Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y. N.; Al-Aizari, F. A.; Ansar, M. Synthesis and pharmacological activities of pyrazole derivatives: A review. *Molecules* **2018**, *23*, 134.

[16]. Halder, A. K.; Moura, A. S.; Cordeiro, M. N. D. S. QSAR modelling: a therapeutic patent review 2010-present. *Expert Opin. Ther. Pat.* **2018**, *28*, 467–476.
[17]. Kausar, S.; Falcao, A. O. An automated framework for QSAR model building. *J. Cheminform.* **2018**, *10*, 1.
[18]. Muhammad, U.; Uzairu, A.; Ebuka Arthur, D. Review on: quantitative structure activity relationship (QSAR) modeling. *J. Anal. Pharm. Res.* **2018**, *7*, 240–242.
[19]. Wang, C.-R.; Wang, Z.-F.; Shi, L.; Wang, Z.-C.; Zhu, H.-L. Design, synthesis, and biological evaluation of pyrazole derivatives containing acetamide bond as potential BRAF V600E inhibitors. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2382–2390.
[20]. ACD/ChemSketch, version 14.01, Advanced Chemistry Development, Inc. (ACD/Labs), Toronto, ON, Canada, www.acdlabs.com (accessed June 2, 2022).
[21]. Molecular Operating Environment (MOE), 2009.10 Chemical Computing Group ULC, 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2022.
[22]. Berman, H. M.; Henrick, K.; Nakamura, H. Announcing the worldwide Protein Data Bank Nature Structural Biology 10 (12): 980, 2003, https://www.rcsb.org/structure/5JRQ (accessed June 2, 2022).