European Journal of Chemistry

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QSAR and molecular docking studies on 4-quinoline carboxylic acid derivatives as inhibition of vesicular stomatitis virus replication

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RESEARCH ARTICLE

10.5155/eurjchem.10.1.45-51.1795

Received: 04 October 2018
Received in revised form: 10 November 2018
Accepted: 12 November 2018
Published online: 31 March 2019
Printed: 31 March 2019

KEYWORDS

PLS
QSAR
Docking study
Vesicular stomatitis virus
4-Quinoline carboxylic acid
Dihydroorotate dehydrogenase

ABSTRACT

The current study describes the development of in silico models based on quantitative structure-activity relationship (QSAR) analysis has been performed on 4-quinoline carboxylic acid derivatives as inhibition capacity of vesicular stomatitis virus replication in Madin Darby canine kidney epithelial cells. A highly descriptive and predictive QSAR model was obtained through the calculation of alignment-independent descriptors using MOE 2009.10 software. For a training set of 20 compounds, the partial least squares analyses result in a model which displays a squared correlation coefficient (r^2) of 0.913. Validation of this model was performed using leave-one-out (q^2) of 0.842. This model gives (r^2_{pre}) of 0.889 for a test set of five compounds. Docking studies were performed for 25 compounds to investigate the mode of interaction between 4-quinoline carboxylic acid derivatives and the active site of the human dihydroorotate dehydrogenase.

Cite this: *Eur. J. Chem.* **2019**, *10(1)*, 45-51 **Journal website**: www.eurjchem.com

1. Introduction

Vesicular stomatitis virus (VSV) is an enveloped, non-segmented, negative-stranded RNA virus and the prototype member of the family Rhabdoviridae, genus *Vesiculovirus* [1,2]. Clinical disease presents as severe vesiculation and/or ulceration of the tongue, oral tissues, feet, and teats, and results in substantial loss of productivity. Except for its appearance in horses, it is clinically indistinguishable from foot-and-mouth disease. Unlike foot-and-mouth disease, it is very infectious for man and can cause a temporarily debilitating disease [3]. The VSV and its membrane glycoprotein G (VSVG) are often used as models to study endocytosis and secretory traffic. For the same reasons, VSVG is often used for pseudo typing of retroviral vectors for gene delivery [4]. VSV is an oncolytic virus currently being investigated as a promising tool to treat cancer because of its ability to selectively replicate in cancer cells [5].

In the following, we have focused on dihydroorotate dehydrogenase (DHODH), the fourth enzyme in the de novo pyrimidine nucleosides biosynthetic pathway [6-8]. Pyrimidine nucleotides play a critical role in cellular metabolism serving as activated precursors of RNA and DNA, CDP diacylglycerol phosphoglyceride for the assembly of cell membranes and UDP-sugars for protein glycosylation and glycogen synthesis [9]. Therefore, DHODH considered as a key enzyme in biosynthesis pathway in most prokaryotic and eukaryotic cells [10]. The therapeutic potential of inhibiting de novo pyrimidine biosynthesis at the dihydroorotate dehydrogenase catalyzed step was revealed by the antiproliferative agents' leflunomide and brequinar (6-fluoro-2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylquinoline-4-carboxylic acid) [11].

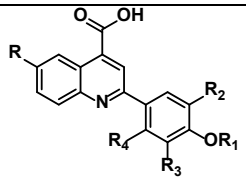
Recently, Das *et al.* reported the 4-quinoline carboxylic acid derivatives as antiviral activity and also tested the ability of these compounds to inhibit *in vitro* VSV replication in Madin Darby canine kidney (MDCK) epithelial cell [12]. In this work, we collected brief group of 4-quinoline carboxylic acid derivatives with biological activity to QSAR study to obtain model, which was used to predict the biological against VSV replication as human DHODH inhibitor and disclosed to docking these derivatives in the target enzyme for the antiviral activity to be human DHODH.

2. Experimental

2.1. QSAR study

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.10.1.45-51.1795

Table 1. Experimental EC_{50}, experimental pEC_{50}, predicted pEC_{50} and residual values of quinoline derivatives of 25 compounds used in training and test sets for inhibit *in vitro* VSV replication in MDCK epithelial cells *.



No	Compound	R	R^1	R^2	R^3	R^4	EC_{50} (μM) (Exp.)	pEC_{50} (Exp.)	pEC_{50}, (Predicted)	Residual
1	Brequinar	F	See Figure 1				0.3	6.52	6.61	-0.09
2	C1	Cl	$(CH_2)_2CH_3$	H	H	H	4.7	5.33	5.52	-0.19
3	C2	Cl	CH_3	H	H	H	7.1	5.15	4.99	0.16
4	C3	Cl	CH_2CH_3	H	H	H	5.7	5.24	4.97	0.27
5	C4 T	Cl	$(CH_2)_3CH_3$	H	H	H	6.3	5.20	5.49	-0.29
6	C11 T	Cl	Ph	H	H	H	1.3	5.89	7.18	-1.29
7	C12	F	Ph	H	H	H	0.1	7.00	6.55	0.45
8	C16	NO_2	Ph	H	H	H	2.0	5.70	5.41	0.29
9	C18	H	Ph	H	H	H	1.0	6.00	6.50	-0.50
10	C22	F	CH_3	H	H	H	6.4	5.19	5.05	0.14
11	C24	F	$(CH_2)_2CH_3$	H	H	H	19.0	4.72	5.25	-0.53
12	C26 T	F	$CH_2(C_2H_5)$	H	H	H	6.8	5.16	5.17	0.01
13	C29	F	Ph-4-NO_2	H	H	H	4.9	5.31	5.53	-0.22
14	C30	F	Ph-3,4-(OCH_3O)	H	H	H	0.9	6.04	6.23	0.19
15	C31	F	Ph-2-F	H	H	H	0.3	6.52	5.94	0.58
16	C32	F	Ph-3-F	H	H	H	0.1	7.00	7.04	-0.04
17	C33 T	F	Ph-4-F	H	H	H	1.0	6.00	6.81	-0.81
18	C34	F	Ph-2-pyridyl	H	H	H	22.9	4.64	4.64	0.00
19	C35	F	Ph-3-pyridyl	H	H	H	2.5	5.60	5.73	-0.13
20	C36	F	Ph-2-thiazolyl	H	H	H	14.6	4.84	4.91	-0.07
21	C39	F	CH_2-Ph	H	H	H	0.232	6.69	6.56	0.13
22	C40 T	F	3,5-Dimethylphenyl	H	H	H	0.522	6.28	7.06	-0.78
23	C42	F	Ph-3-$C(CH)_3$	H	H	H	0.062	7.18	7.66	-0.48
24	C43	F	Ph	CH_3	CH_3	H	0.023	7.63	7.73	-0.10
25	C44	F	Ph	$CH(CH_3)_2$	H	CH_3	0.002	8.69	8.18	0.51

* T = Test set.

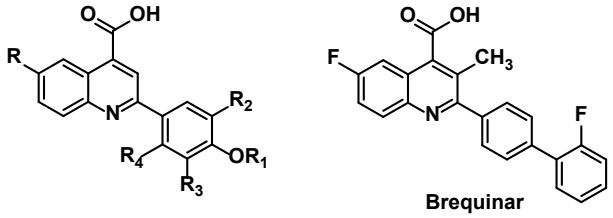


Figure 1. Basic structure 4-quinoline carboxylic acids derivatives and brequinar.

2.1.1. Data set

The set of selected compounds reported by Das *et al.* [12] was used to QSAR study. Only 25 compounds have were selected from three combine set according to which that compounds have F, Br, and H atom in position R, and also phenyl, alkyl and heterocycle group in position R^1. Structure of compound with substitution of R and R^1 position and their biological activity as inhibit *in vitro* VSV replication in MDCK epithelial cells were reported (Figure 1).

These compounds were evaluated for their ability to inhibit VSV replication in MDCK epithelial cells in terms of half maximal effective concentration (EC_{50}) values. For the purpose of modeling study, all 25 derivatives have been divided into training and test sets. Out of the 25 derivatives fifth compounds have been placed in the test set for the validation of derived models. The biological activities of 25 compounds transformation to pEC_{50}, see Table 1.

2.1.2. Theoretical molecular descriptors

The compounds of training and test set were first drawn using ACD/Lab (Copyright 1994-2010, ACD/Labs 12.00, product Version 12.01, Build 36726, 26Feb 2010) freeware and saved in "mol" file format. Then, the saved file was opened by MOE 2009.10 were minimized energy, the different molecular 25 descriptors were calculated and decrease the redundancy existing in the descriptors data matrix, the correlations of descriptors with each other and with pEC_{50} of the molecules are examined, and collinear descriptors ($r < 0.9$) are detected. Those descriptors which have the pairwise correlation coefficient above 0.9 and having the lower correlation with pEC_{50} values are removed from the data matrix [13].

Eight descriptors were left in clouding Log octanol/water partition coefficient (Log $P_{o/w}$), molar refractivity (mr), heat of formation (AM1-HF), dipol moment (AM1-Dipol), total polar surface area (ASA-P), atomic connectivity index order zero (Chi_0), mass density (Density) and ionization potential (AM1-IP). The values of descriptors were listed in Table 2.

2.1.3. Model development

The QSAR models were constructed based on the partial least square method using to descriptors in MOE 2009.10 software. QSAR was built using the descriptor as an independent variable and EC_{50} as a dependent variable by forward stepwise regression analyses. QSAR equations were acquired according to different combinations of various descriptors. The data matrix was analyzed using the partial least squares (PLS) method.

Table 2. The values of molecular descriptor of training and test sets compounds *.

No	Compound	AM1-Dipole	AM1-HF	AM1-IP	ASA-P	Chi_0	mr	Log $P_{(o/w)}$	Density
1	Brequinar	4.82	-86.57	8.95	76.12	19.84	10.58	7.40	0.76
2	C1	3.39	-63.08	8.90	113.38	17.10	9.50	5.28	0.78
3	C2	2.96	-50.81	8.93	142.51	15.69	8.55	4.33	0.80
4	C3	3.25	-56.28	8.89	115.68	16.40	9.02	4.67	0.79
5	C4 ^{T}	2.30	-10.72	8.97	104.69	18.80	10.57	5.98	0.78
6	C11 ^{T}	2.18	-48.26	8.94	102.78	18.80	10.14	5.54	0.77
7	C12	5.37	1.97	9.26	187.70	20.38	10.59	5.32	0.79
8	C16	2.45	-3.20	8.93	104.83	17.93	10.07	5.35	0.73
9	C18	1.56	-88.06	8.93	142.71	15.69	8.12	3.89	0.78
10	C22	2.59	-99.27	8.85	113.75	17.10	9.07	4.84	0.76
11	C24	3.90	-72.52	8.89	159.81	17.97	9.45	5.01	0.76
12	C26 ^{T}	4.79	-43.76	9.35	188.86	21.25	10.66	5.48	0.82
13	C29	2.14	-103.4	8.90	156.98	20.66	10.72	5.25	0.80
14	C30	3.00	-91.77	9.03	104.41	19.67	10.18	5.69	0.80
15	C31	1.43	-93.74	9.08	102.43	19.67	10.17	5.73	0.80
16	C32	1.37	-90.91	9.02	104.58	19.67	10.17	5.69	0.80
17	C33 ^{T}	3.79	-26.18	9.20	125.27	18.80	9.98	4.71	0.78
18	C34	1.54	-38.35	9.10	123.41	18.80	9.98	4.31	0.78
19	C35	2.80	21.34	9.17	135.70	18.10	9.84	4.52	0.83
20	C36	2.43	-59.56	8.87	117.75	19.51	10.62	5.68	0.76
21	C39	2.59	-63.06	8.93	102.59	20.54	11.04	6.25	0.75
22	C40 ^{T}	1.74	-28.34	8.74	104.74	21.37	11.75	6.76	0.76
23	C42	2.99	-67.37	8.88	106.26	22.17	11.94	7.04	0.73
24	C43	1.35	-60.40	9.11	104.60	20.54	11.05	6.21	0.75
25	C44	1.94	-70.03	8.92	101.77	22.12	11.97	7.05	0.73

* T = Test set.

The quality of each regression model was evaluated using a squared correlation coefficient (r^2 > 0.7) and root mean square error (RMSE) [14]. Finally, to exclude false or artificial correlations, the external consistency of the variables of the model have been addressed in terms of cross-validated r^2 or q^2 (>0.5) criteria from the leave-one-out (LOO) cross-validation procedure as default option. The coefficient r^2 indicated how well the equation fits the data. The q^2 was considered as an indicator of the predictive performance and stability of a QSAR mode [15]. About ten QSAR models were generated by using partial least square regression method coupled with stepwise forward backward method. Among the various models two significant QSAR models were finally selected. Models summary of best models are given below.

2.1.4. Validation model

Validation is a crucial and important aspect for the determination of the reliability of models [16]. In this study, the data set is divided into training set for model development and test set for external prediction. Goodness of fit of the models was assessed by examining the multiple correlation coefficient r^2, the standard deviation (s), the F-ratio between the variances of calculated and observed activities (F) [15,17].

2.2. Docking study

Twenty five ligands of 4-quinoline carboxylic acid derivatives "mol" file format were opened in Molecular Operating Environment (MOE 2009.10). The 3-D protonated structures of compound were energy minimized. Then, 25 compounds have been compute conformational and saved in a molecular database (mdb) file for further studies.

The crystal structure of the complex of human dihydro-orotate dehydrogenase protein (PDB code: 1D3G) was retrieved from a protein data bank. The pdb file was imported to MOE suite where receptor preparation module was used to prepare the protein. All the bound water molecules were removed from the complex. 3D protonation and the active site identification were done. MOE Docking Simulation Program was used to perform the total of ten independent docking runs. The docked poses were inspected and the top scored pose for each compound was reserved for further studies of interaction evaluation. The ligand-protein interactions were visualized in 2-dimensional space by making use the MOE Ligand Interactions Program [17].

3. Results and discussion

3.1. QSAR results

As the number of 4-quinoline carboxylic acid derivatives in the training set was 20, it was important to reduce the number of descriptors until the ratio was ≦ 4. After eight descriptors (Log $P_{o/w}$, mr, AM1-HF, AM1-Dipol, ASA-P, Chi_0, Density and AM1-IP) were selected. The correlation between the selected descriptors and pEC_{50} was established. The value of the correlation coefficient for each pair of selected descriptors was examined. The greatest value of the correlation coefficient (0.859) is that belonging to the pair of descriptors Log $P_{o/w}$ and AM1-Dipol.

The models obtained for the prediction of inhibitory concentration of 4-quinoline carboxylic acid derivatives, using 25 compounds, with highest significant models in four descriptors are given below:

$$pEC_{50} = 0.11131 - 0.56687\times AM1\text{-}Dipole + 1.12247\times Log\ P_{o/w} + 0.00702\times AM1\text{-}HF + 0.00732\times ASA.P \quad (1)$$

$$pEC_{50} = 1.38478 - 0.49189\times AM1\text{-}Dipole + 0.85383\times Log\ P_{o/w} + 0.00642\times AM1\text{-}HF + 0.09659\times Chi_0 \quad (2)$$

$$pEC_{50} = 1.40898 - 0.47655\times AM1\text{-}Dipole + 0.85460\times Log\ P_{o/w} + 0.00565\times AM1\text{-}HF + 0.170832\times mr \quad (3)$$

The four relevant descriptors (variables) in Equations (1, 2 and 3) of 25 compound ($n_{training}$ = 20 and $n_{test\ set}$ = 5) could explain 91.3, 90.4 and 89.7% of the variance (adjusted coefficient of variation) of the inhibitory concentration. The difference between r^2 and q^2 of three models were be < 0.1. These differences were less than 0.3, signifying the robustness of the models. The values of all the statistical parameters being within the acceptable limit reflect the internal and external predictive potential of the developed models [18]. Root mean square error (RMSE) and standard error of estimate (SEE) were lower value is better for both to good model. These two values are lower and acceptable F (F-test) or *p*-value showed value higher, so this is batter for models.

Table 3. The statistical parameter for fives equations.

Equation	$n_{training}$	$n_{test\ set}$	r^2	q^2	r^2_{Pred}	RMSA	F-value	*p*-value	SEE
1	20	5	0.913	0.842	0.889	0.311	39.283	<0.0001	0.359
2	20	5	0.904	0.821	0.902	0.328	35.064	<0.0001	0.379
3	20	5	0.897	0.805	0.885	0.337	32.776	<0.0001	0.390
4	20	5	0.891	0.804	0.855	0.348	43.641	<0.0001	0.389
5	20	5	0.859	0.782	0.894	0.397	51.702	<0.0001	0.429

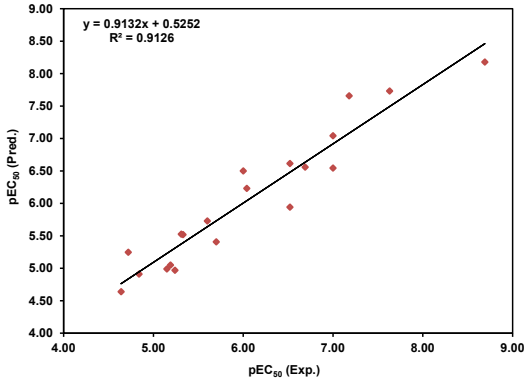


Figure 2. Plot of predicted training set versus experimental pEC_{50} values.

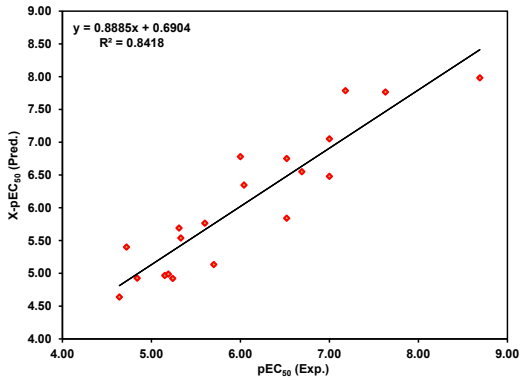


Figure 3. Plot of cross validation prediction (X-pEC_{50}) versus experimental pEC_{50} values.

The highest significant models in three and two descriptors are given also below:

$$pEC_{50} = 2.43728 - 0.49571\times AM1\text{-}Dipole + 1.01033\times Log\ P_{o/w} + 0.00731\times AM1\text{-}HF \quad (4)$$

$$pEC_{50} = 2.00731 - 0.42239\times AM1\text{-}Dipole + 0.95099\times Log\ P_{o/w} \quad (5)$$

The three and two relevant descriptors (variables) in Equations (4 and 5) showed Criteria Model signifying the robustness of the two models. Summary of the all statistical parameter for fives equations reported in Table 3.

The plot showing goodness of fit between observed and calculated activities for the training and test set compounds is given in Figure 2-4 for the best model. The QSAR model of Equation (1) was developed using 25 compounds as training set and test set molecules in Table 1.

3.2. Docking results

To develop a deeper insight into the molecular mechanism of 4-quinoline carboxylic acid derivatives as human dihydro-orotate dehydrogenase comprising, the compounds brequinar (Reference), C12, C32, C42, C43 and C44 were simulated computationally to the active sites of human DHODH protein (PDB code: 1D3G). Human DHODH protein consisted of active site as shown in Figure 5.

In silico molecular docking results, produced the different docking conformations based on binding energy. The variants with the minimal energy of the enzyme-inhibitor complex were selected for studies of binding mode. Preferred docked conformations of most of the ligands formed one cluster inside the active [19].

All the docked conformations for each compound were analyzed and it was found that the most favorable docking poses with maximum number of interactions were those which were ranked the highest based on the minimal binding energy, which was computed as a negative value by the software. The most favorable docking poses of the 25 docked conformations for each compound were analyzed to further investigate the interactions of the docked conformations within the active sites. The detailed docking results are tabulated in Table 4.

The active site consisted of hydrophilic amino acids (His56, Tyr63, Tyr356, Tyr380, Arg136 and Gly 97) and the hydrophobic portions were constructed (Ala55, Ala59, Val134, Val62, Leu46, Leu67, Leu68, Leu359, Met43, Phe62, Pro52 and Pro364). Mostly ligands showed strong three polar interactions between two oxygen atoms in carboxylic group with hydrogen atom of amino group in Arg136 and Gln47 as hydrophilic interaction Figure 6.

Table 4. Free binding energy (kJ/mol), bond interaction and interacted amino acid of the investigated compounds.

No	Compound	Free binding energy, S	Type of bond interacted	Interaction group	Amino acid interacted	Length (Å)
1	Brequinar analog *	-42.43	3 Polar bonds	H-O of carboxylic acid	Arg136	1.32
				H-O of carboxylic acid	Gln47	1.62
				C=O of carboxylic acid	Arg136	1.27
2	Brequinar **	-35.03	3 Polar bonds	H-O of carboxylic acid	Arg136	1.68
				C=O of carboxylic acid	Gln47	1.87
				C=O of carboxylic acid	Arg136	1.89
3	C1	-28.91	1 Polar bonds	C=O of carboxylic acid	Arg 136	2.10
4	C2	-15.54	π-Interaction	Phenyl	Phe62	-
5	C3	-38.19	3 Polar bonds	H-O of carboxylic acid	Arg136	1.90
				C=O of carboxylic acid	Gln47	1.92
				C=O of carboxylic acid	Arg136	1.85
6	C4	-39.67	3 Polar bonds	H-O of carboxylic acid	Arg136	1.85
				C=O of carboxylic acid	Gln47	1.96
				C=O of carboxylic acid	Arg136	1.85
7	C11	-41.81	3 Polar bonds	H-O of carboxylic acid	Arg136	1.85
				C=O of carboxylic acid	Gln47	1.94
				C=O of carboxylic acid	Arg136	1.81
8	C12	-42.31	3 Polar bonds	H-O of carboxylic acid	Arg136	1.75
				H-O of carboxylic acid	Gln47	1.97
				C=O of carboxylic acid	Arg136	1.81
9	C16	-42.51	3 Polar bonds	H-O of carboxylic acid	Arg136	1.78
				H-O of carboxylic acid	Gln47	1.92
				C=O of carboxylic acid	Arg136	1.83
10	C18	-42.02	3 Polar bonds	H-O of carboxylic acid	Arg136	1.98
				H-O of carboxylic acid	Gln47	1.74
				C=O of carboxylic acid	Arg136	1.83
11	C22	-36.34	3 polar bonds	H-O of carboxylic acid	Arg136	1.98
				H-O of carboxylic acid	Gln47	1.79
				C=O of carboxylic acid	Arg136	1.81
12	C24	-38.67	3 Polar bonds	H-O of carboxylic acid	Arg136	1.82
				C=O of carboxylic acid	Gln47	1.92
				C=O of carboxylic acid	Arg136	1.77
13	C26	-39.10	3 Polar bonds	H-O of carboxylic acid	Arg136	1.73
				C=O of carboxylic acid	Gln47	2.07
				C=O of carboxylic acid	Arg136	1.75
14	C29	-17.56	1 Polar bonds	C=O of carboxylic acid	Tyr265	3.69
15	C30	-43.85	3 Polar bonds	H-O of carboxylic acid	Arg136	1.82
				C=O of carboxylic acid	Gln47	1.97
				C=O of carboxylic acid	Arg136	1.77
16	C31	-43.28	3 Polar bonds	H-O of carboxylic acid	Arg136	1.80
				C=O of carboxylic acid	Gln47	1.97
				C=O of carboxylic acid	Arg136	1.75
17	C32	-43.06	3 Polar bonds	H-O of carboxylic acid	Arg136	1.75
				H-O of carboxylic acid	Gln47	1.96
				C=O of carboxylic acid	Arg136	1.81
18	C33	-47.29	3 Polar bonds	H-O of carboxylic acid	Arg136	1.95
				H-O of carboxylic acid	Gln47	1.77
				C=O of carboxylic acid	Arg136	1.89
19	C34	-41.81	3 Polar bonds	H-O of carboxylic acid	Arg136	1.75
				H-O of carboxylic acid	Gln47	1.96
				C=O of carboxylic acid	Arg136	1.82
20	C35	-41.41	3 Polar bonds	H-O of carboxylic acid	Arg136	1.75
				C=O of carboxylic acid	Gln47	1.96
				C=O of carboxylic acid	Arg136	1.82
21	C36	-41.58	3 Polar bonds	H-O of carboxylic acid	Arg136	1.82
				C=O of carboxylic acid	Gln47	1.96
				C=O of carboxylic acid	Arg136	1.76
22	C39	-42.23	3 Polar bonds	H-O of carboxylic acid	Arg136	1.75
			π-Interaction	C=O of carboxylic acid	Gln47	1.99
				C=O of carboxylic acid	Arg136	1.81
				Phenyl	Phe62	-
23	C40	-37.76	3 Polar bonds	H-O of carboxylic acid	Arg136	1.83
				C=O of carboxylic acid	Arg136	1.67
24	C42	-45.40	3 Polar bonds	H-O of carboxylic acid	Arg136	1.83
				C=O of carboxylic acid	Gln47	1.97
				C=O of carboxylic acid	Arg136	1.77
25	C43	-39.33	3 Polar bonds	H-O of carboxylic acid	Arg136	1.73
				C=O of carboxylic acid	Gln47	2.02
				C=O of carboxylic acid	Arg136	1.73
26	C44	-29. 71	3 Polar bonds	H-O of carboxylic acid	Arg136	2.19
			π-Interaction	C=O of carboxylic acid	Gln47	2.05
				C=O of carboxylic acid	Arg136	1.95
				Phenyl	Phe62	-

* 2-Biphenyl-4-yl-6-fluoro-3-methyl-quinoline-4-carboxylic acid.
** 6-Fluoro-2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methylquinoline-4-carboxylic acid.

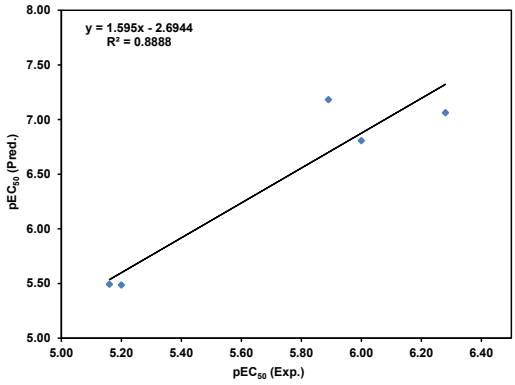


Figure 4. Plot of predicted test set versus experimental pEC_{50} values.

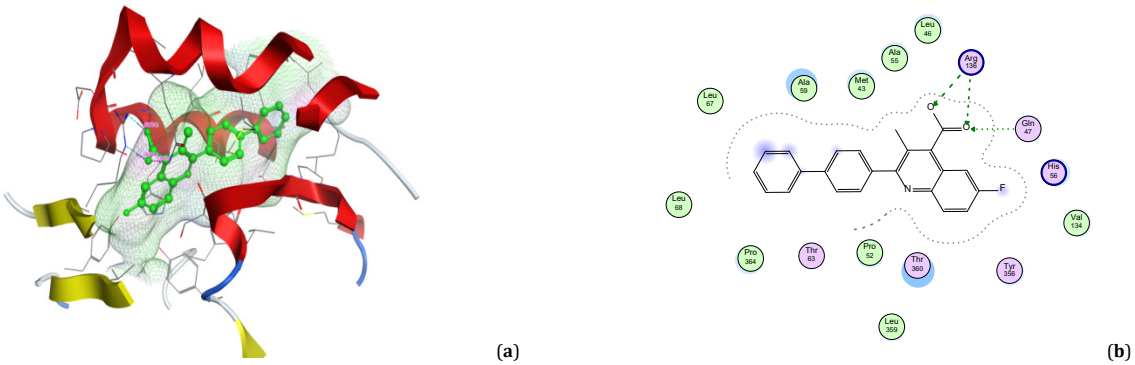


Figure 5. (**a**) 3D model of active sites of human DHODH protein 1D3G with brequinar analog ligand, (**b**) 2D model of ligand interaction with protein.

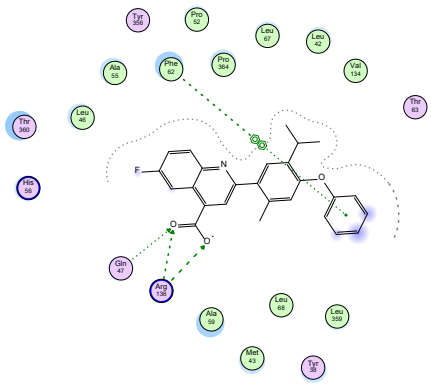


Figure 6. 2D model of compound C44 interactions by π-interaction with Phe62 and three hydrogen bonding interactions with Arg136 and Gln47.

Strong hydrogen bonding interactions of ligands with Arg136 and Gln47 showed bond distances in range (1.32 and 2.10 Å). It is quite interesting to note that the binding free energies "S" in Escore-1 (London dG) for all ligands are in the range difference between them from -35.031 to -45.400 kcal/mol, except compounds C1m, C2 and C29 showed lower binding free energy. Compounds C42, C30, C31 and C32 showed binding free energies (-45.400, -43.835, -43.278 and -43.059 kcal/mol, respectively) higher than reference analogues Brequinar (-42.4287 kcal/mol). This may explain the higher activity of them compared to analogues Brequinar. Although compound C44 showed higher biological activity than the others, it has lower binding free energy (-29.708 kcal/mol). The π-interaction between phenyl ring in compound C44 and phenyl ring in Phe62 beside to three hydrogen bonding interactions mentioned above, maybe that explains the higher activity of compound C44 than other compounds (Figure 6).

4. Conclusion

The derived QSAR models have provided rationales to explain of 4-quinoline carboxylic acid derivatives inhibitory activity to VSV replication, according to descriptors; Log $P_{o/w}$, mr, AM1-HF, AM1-Dipol, ASA-P, Chi_0, density and AM1-P; by highlighted the role of these descriptors in biological activity. PLS analysis has also confirmed the suggested models have acceptable predictability. All the compounds are within the applicability domain of the proposed models and were evaluated correctly. These models can be used to design new

4-quinoline carboxylic acid derivatives as inhibitors of human dihydroorotate dehydrogenase. The binding energies derived from docking simulations indicated that almost all the 25 compounds are exhibited stronger binding affinity for 1D3G. It is noteworthy, the higher biological activity of diaryl ether substituted 4-quionline carboxylic acid as inhibitors human as dihydroorotate dehydrogenase reported by Das *et al*. be through with result of docking [12]. In the view of this study, the further research can be carried on the newly designed compound, which has diaryl ether substituted 4-quinoline carboxylic acid, as inhibitors.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.

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