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QSAR modeling of novel substituted 4-Phenylisoquinolinones as potent BET bromodomain (BRD4-BD1) inhibitors

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Abstract

Drugs that can combat cancer are very important in the quest to eradicate the scourge, amongst which are the BRD1-BD1 inhibitors. QSAR study was carried out on forty compounds of substituted 4-phenylisoquinolinones in order to predict the ability of some compounds as (BRD4-BD1) inhibitors through mathematical models. Genetic Function Approximation (GFA) method was employed to generate four different models. The first model generated was the best owing to its significance, statistically. The best model has a Coefficient of determination (R^2) of 0.93, Cross validation coefficient (Q^2_{ev}) of 0.70, Coefficient of determination for Y-randomization (cR^2_p) of 0.85. Furthermore, the built model was validated externally by R^2_{pred} = 0.95 which endorsed its predictive strength. This was further validated by applicability domain to check for outliers and influential compounds and two compounds were detected to be influential as their leverage values were higher than the warning limit (h = 0.54). Due to the reliability, stability and robustness of the built model, some compounds were designed and predicted to have improved activity as potent BET Bromodomain (BRD4-BD1) inhibitors. Thus, these compounds could be useful as anticancer and anti-inflammatory agents.

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Introduction

Bromodomain and Extra -Terminal motif (BET) consists of protein BRDT, BRD2, BRD3 and BRD4. The BET – acetylated histone interactions are prevented by a class of drug called BET inhibitors [1]. The first BET inhibitors synthesized were thionodiazepine [2], JQ-1 and benzodiazepine I-BET 762 [3]. Recently, a lot of compounds have been synthesized and tested to inhibit the activity of BET bromodomain [4]. Till date, there is no BET inhibitor that can reasonably distinguish between the members of BET family (BRDT, BRD2, BRD3 and BRD4) [5]. BRD4, a member of BET family consists of two bromodomain just like other members (BD1 and BD2).

Due to the interaction with P-TEFb through its domain (P-TEFb interaction domain, PID) and also its ability to stimulate kinase activity and RNA polymerase II through carboxyl terminal domain (CTD) [6], BRD4 has been the major target for BET inhibitors [7-9]. BRD4 also interact with JMJD6 [10], GATA1 [11], and RFC (1-5) [12]. Other selected examples of BRD4 inhibitors include MS4 17 [13], I-BET 762 [8], CPI-203 [14] and RVX -208 [15].

Despite the clinical evaluation of numerous compounds as BET inhibitors, many are still under observation [16]. In an attempt to solve the problem of cost and time in experiments, Quantitative Structure Activity Relationship (QSAR), with the aid of computational and statistical software has been employed as a predictive tool in predicting the activity of compounds. A lot of compounds have been developed with this quantitative method and researches are been done daily in order to solve more real-world problems pertaining to health. QSAR aims at correlating the molecular properties of the compound with its biological activities such as inhibition concentration [17].

Due to the resistance of tumor cells to existing inhibitors, there will always be need to synthesize BET inhibitors to combat the activity of these tumor cells. [18]. Therefore, this work aimed at designing some compounds as potent (BRD4-BD1) using a mathematical model obtained through QSAR technique.

Recent BET inhibitors synthesized may create a pathway to future generation of BET inhibitors as parent compounds [16].

Materials and method

Data collection

For this study, forty compounds of substituted 4-Phenylisoquinolinone derivatives [19] as BET bromodomain inhibitors were compiled from the literature. The *in vivo* curative activities of the target chemical compounds against BRD4-BD1 given in IC_{50} (µM) were converted into their corresponding negative logarithm pIC_{50} values (i.e - log IC_{50} = pIC_{50}) in order to make the activity conform to a range of values and to also suit normal distribution curve. In Table 1, we present the experimental activities, pIC_{50} values and the representative compounds.

Geometry Optimization

The cdx file format of the compounds drawn using ChemDraw Ultra 12.0 were exported to Spartan 14 for further optimisation using Molecular Mechanics Force Field (MMFF) followed by Density Functional Theory (DFT) applying the Becke three Lee-Yang-Parr (B3LYP) correlation and 6-31G* basis set [20,21].

Molecular Descriptor Calculation

PaDEL-Descriptor software was used to calculate the 1D, 2D and 3D descriptors of the compounds. After removing salt, detecting tautomer and retaining the file name as molecule name, the descriptors were saved as Microsoft Excel Comma Separated value (csv) file.

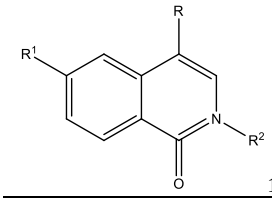
Normalization and Data pre-treatment

The calculated descriptors were normalized for all the compounds (Eq. 1) enabling equal opportunity for each variable in influencing the model, an important step in developing a good model [22].

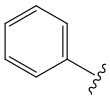
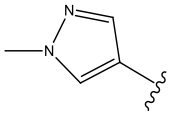
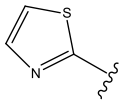
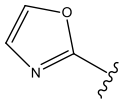
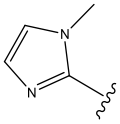
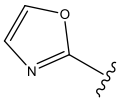
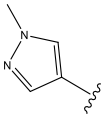
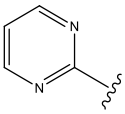
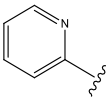
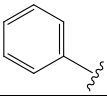
$$X = \frac{X_1 - X_{min}}{X_{max} - X_{min}} \quad 1$$

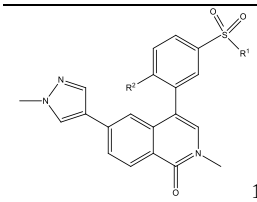
where X_1 , X_{min} and X_{max} represents the descriptor's value, descriptor's minimum and maximum values respectively. Pre-treatment of the normalized data was then done using Data Pre-treatment software from Drug Theoretical and Cheminformatics Laboratory (DTC Lab). This is done to generate descriptors with high correlated data and also reduce colinearity which will help in improving the prediction performance of the model.

Table 1: Structure of substituted isoquinolinone derivatives and their activities against BRD4-BD1.



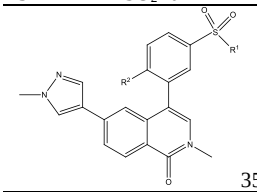
1-17

S/No	R	R^1	R^2	Experimental activity pIC_{50}(μM)	Predicted activity pIC_{50}(μM)	Residual
1	$COCH_3$	H	Me	4.15	3.83	0.32
2	$COCH_3$		Me	4.09	4.13	-0.03
3	$COCH_3$		Me	4.62	4.10	0.52
4	$COCH_3$		Me	3.92	4.19	-0.27
5	$COCH_3$		Me	4.14	4.06	0.09
6	CONHMe	H	Me	4.82	4.53	0.30
7	CONHEt	H	Me	4.31	4.78	-0.47
8	CONHBn	H	Me	4.59	4.47	0.12
9	CO_2Me	H	Me	4.52	4.11	0.42
10	CO_2Me	H	Et	4.05	4.18	-0.13
11	CO_2Me	H	nPr	3.70	4.22	-0.52
12		H	Me	4.70	5.07	-0.37
13		H	Me	4.89	5.01	-0.12
14		H	Me	5.80	5.09	0.71
15		H	Me	4.94	5.08	-0.14
16		H	Me	5.02	5.11	-0.09
17		H	Me	5.47	5.14	0.32



18-34

S/No	R	R^1	Experimental activity pIC_{50}(μM)	Predicted activity pIC_{50}(μM)	Residual
18	SO_2NH_2	H	6.29	6.40	-0.11
19	SO_2NHEt	H	6.15	6.42	-0.27
20	SO_2NHBn	H	5.52	6.26	-0.73
21	$NHSO_2Me$	H	6.62	6.38	0.24
22	$NHSO_2Et$	H	6.80	6.28	0.51
23	$NHSO_2Pr$	H	6.39	6.39	0.00
24	$NHSO_2Bu$	H	6.38	6.39	-0.01
25	NH2	H	5.54	5.17	0.37
26	$NMeSO_2Me$	H	6.34	6.39	-0.06
27	CH_2NHSO_2Me	H	6.12	6.37	-0.25
28	$NHSO_2NMe_2$	H	6.60	6.39	0.22
29	$NHSO_2Me$	Me	6.82	6.50	0.32
30	$NHSO_2Me$	Et	6.57	6.56	0.01
31	$NHSO_2Me$	Ph	6.04	6.68	-0.64
32	$NHSO_2Me$	1-Methylpyrazol-4-yl	7.30	6.67	0.64
33	SO_2Et	H	6.04	6.41	-0.37
34	SO_2Et	1-Methylpyrazol-4-yl	6.87	6.70	0.17



35-40

S/No	R^1	R^2	Experimental activity pIC_{50}(μM)	Predicted activity pIC_{50}(μM)	Residual
35	Et	OMe	7.82	7.63	0.19
36	Et	OEt	8.30	8.42	-0.12
37	Et	OnPr	8.52	8.31	0.22
38	Et	$OCH_2CH_2NH_2$	7.31	7.16	0.15
39	Me	OEt	8.05	8.39	-0.35
40	Me	OnPr	8.30	8.29	0.01

Data Division

The pre-treated dataset was divided into training and test sets via the Kennard and Stone's algorithm [23]. The training set comprises of 70% of the data sets (28 compounds) which was used to build the model and validated internally while 30% of the data sets (12 compounds) were used for external validation.

Model building

Material studio 2017 software was used to build the model via Genetic Function Approximation (GFA) method with in vivo curative activities (pIC_{50}), the dependent variable and descriptors (physiochemical properties), the independent variables.

Internal validation of model

The models generated were appraised with the Friedman formula (LOF) to obtain their fitness scores and defined as; [24].

$$LOF = \frac{SEE}{\left(1-\frac{C+dp}{M}\right)^2} \qquad 2$$

SEE represents the standard error of estimation, p represents the total number of descriptors in the model, d represents a user-defined smoothing parameter, c represents the number of terms in the model, and M represents the number of compounds in the training set [25].

SEE equates to the standard deviation. A model is deemed good if it has low SEE (equation 3) value.

$$SEE = \sqrt{\frac{\left(Y_{exp}-Y_{pred}\right)^2}{N-P-1}} \qquad 3$$

The correlation coefficient (R^2) is the most commonly used parameter in assessing a QSAR model internally. A generated model is said to be good when the value of R^2 is closer to 1.0. The correlation coefficient (R^2) is given as:

$$R^2 = 1 - \frac{\Sigma(Y_{exp} - Y_{pred})^2}{\Sigma(Y_{exp} - Y_{training})^2} \quad 4$$

Where Y_{exp}, $Y_{training}$, and Y_{pred} are the experimental activity, mean of the experimental activity and the theoretical activity in the training set respectively.

The value of R^2 varies directly with an increase in the number of descriptors used in building the model. Thus, correlation coefficient (R^2) is not dependable to measure the stability of a model. For this reason, the correlation coefficient (R^2) is modified in order to have a stable and reliable model. The adjusted R^2 is given as:

$$R^2_{adj} = \frac{R^2 - P\,(n-1)}{n - p + 1} \quad 5$$

Given that p and n are number of descriptors and compounds in the model that made up the training set respectively.

Cross validation test was carried out to analyse the strength of the built model in predicting the activity of new compounds. The cross-validation coefficient (Q^2_{cv}) is given as:

$$(Q^2_{cv}) = 1 - \left\{\frac{\Sigma(Y_{pred} - Y_{exp})^2}{\Sigma(Y_{exp} - Y_{training})^2}\right\} \quad 6$$

External validation of the model

The R^2_{test} value is the most commonly used parameter to externally validate a built model despite other parameters because once the R^2_{test} value is considered satisfied, the remaining parameters will also be satisfied. Also, the built model is said to be stable when the value of R^2_{test} is closer to 1.0. This stability will account for the reliability of the model in predicting the activity of a new compound. The R^2_{test} is defined by as:

$$R^2 = 1 - \frac{\Sigma\left(Y_{pred_{test}} - Y_{exp_{test}}\right)^2}{\Sigma\left(Y_{pred_{test}} - \bar{Y}_{training}\right)^2} \quad 7$$

Where $\bar{Y}_{training}$ is mean values of experimental activity of the training set while $Y_{exp_{test}}$ and $Y_{pred_{test}}$ are the experimental activity and predicted test set.

Y-Randomization test

Another method to validate the built model is through Y-Randomization test. The test was performed on the training set data to ensure that the strength of the QSAR model is not by chance [24]. The low values of R^2 and Q^2 generated for several trials is expected to be low to ensure reliability of the model. In addition to R^2 and Q^2, cR^2_p is another important parameter. It must be more than 0.5 before the test could be considered valid. The cR^2_p is defined as:

$$cR^2_p = R \times [R^2 - (R_r)^2]^2$$

Where R is the Coefficient of determination, cR^2_p is the Coefficient of determination for Y-randomization and R_r is the average 'R' of random models for several trial.

Evaluation of the applicability domain of the model

Evaluation of applicability domain of a model is a crucial step in proving that the QSAR model is good to make predictions [26]. Here, the leverage approach was employed [27]. Leverage hi, is defined as (Eq. 9):

$$hi = X_i(X^T X)^{-1} X_i^T \quad 9$$

where X_i represents the training compounds matrix of i. X represents the m × k descriptor matrix of the training set compound and X^T represents the transpose matrix of X which was used to build the QSAR model. The warning leverage (h^*) is the limit of normal values for X outliers and is given as:

$$h^* = 3\frac{(k+1)}{n} \quad 10$$

Where n and k are the descriptors and the training set compounds respectively

Quality assurance of the model

Several validations parameters were employed to measure the strength, dependability and predictive ability of the built model. The general minimum requirement values for both internal and external validation parameters for assessment of a QSAR model is given in **Table 2** [28].

Table 2: Generally recommended value for the validation parameters for a built QSAR model

Parameter	Definition	Recommended value
R^2	Coefficient of determination	≥0.60
$P_{(95\%)}$	Confidence interval at 95% confidence level	<0.05
Q^2_{cv}	Cross validation coefficient	≥0.50
R^2 -Q^2_{cv}	Difference between R^2 and Q^2_{cv}	<0.30
$N_{(ext\ \&\ test\ set)}$	Minimum number of external test set	≥5.00
cR^2_p	Coefficient of determination for Y-randomization	≥0.50

Results

Descriptors Calculation

The Padel Descriptor software was used to generate 1875 molecular descriptors which constitute the chemical information of that encodes the structure activity of forty compounds of substituted 4-Phenylisoquinolinone derivatives as BET bromodomain inhibitors.

QSAR Model and Validation of substituted Isoquinolinone derivatives

The validation parameters for the four different models generated are presented (**Table 3**) and illustrated below:

Model 1

pIC_{50} = 3.035551668 * BCUTp-1l + 0.578503096 * nBondsD2 - 0.807215157 * ndssC + 0.400912822 * maxssO - 10.505769517

Model 2

pIC_{50} = 4.010572155 * BCUTp-1l + 0.499642119 * maxssO - 2.881554624 * MOMI-XY + 3.221171414 * RDF135s - 11.943416905

Model 3

pIC_{50} = 4.822108789 * BCUTp-1l + 0.165983293 * VE3_Dt + 0.699486202 * maxaasN + 0.388855034 * maxssO - 19.084126461

Model 4

pIC_{50} = 1.001062250 * AATS2s + 4.299175312 * BCUTp-1l + 0.825113725 * maxaasN + 0.348257341 * maxssO - 20.744597041

Table 3: Validation Parameters for the models generated from Genetic Function Approximation (GFA)

S/No		Model One	Model Two	Model Three	Model Four
1	Friedman LOF	0.59	0.60	0.61	0.64
2	R-squared	0.93	0.93	0.93	0.92
3	Adjusted R-squared	0.92	0.92	0.91	0.91
4	Cross validated R-squared	0.70	0.88	0.89	0.88
5	Significant Regression	Yes	Yes	Yes	Yes
6	Significance-of-regression F-value	75.85	75.30	73.63	70.08
7	Critical SOR F-value (95%)	2.85	2.85	2.85	2.85
8	Replicate points	0.00	0.00	0.00	0.00
9	Computed experimental error	0.00	0.00	0.00	0.00
10	Lack-of-fit points	23.00	23.00	23.00	23.00
11	Min expt. error for non-significant LOF (95%)	0.30	0.30	0.30	0.31

Table 4: List of Descriptors used in building the QSAR model and their dimension

S/No	Name	Description	Dimension
1	BCUTp-1l	First lowest eigenvalue of burden matrix weighted by polarization	2D
2	nBondsD2	Total number of double bonds (excluding bonds to aromatic bond)	2D
3	ndssC	Number of dssC	2D
4	maxssO	Max of ssO	2D

Statistical Analysis of the Descriptors

The descriptors used in building the best model was further subjected to Pearson's correlation and descriptive statistics to establish how the descriptors depend on each other, statistical parameter of the training and test set and results were presented in **Table 5, 6 & 7**.

The coefficient of determination R^2 for both training set and test is reported in **Figure 1A & B)**. The randomness of the activities on both negative and positive sides of y-axis shown on the scatter plot between Standardized Residual activity and the experimental activity reported in **Figure 1C**. To discover influential and outliers' compounds in the built model, the standardized residual activity for the entire data set was plotted against the leverages and presented in **Figure 1D**.

Design of new Drug

The best model was used to design 5 novel compounds using Substituted 4-Phenylisoquinolinones as a template. The structures, descriptors and predicted activity of the new compounds were presented in **Table 9**.

Table 5: Pearson's Correlation analysis of the descriptors used in the built model

	BCUTp-1l	nBondsD2	NdssC	maxssO
BCUTp-1l	1.00			
nBondsD2	0.06	1.00		
ndssC	-0.35	0.70	1.00	
maxssO	-0.49	0.40	0.43	1.00

Table 6: Descriptive statistics of the inhibition data

Statistical parameters	Activity	
	Training set	Test set
Mean	5.82	5.96
Standard Error	0.24	0.45
Median	5.92	6.33
Standard Deviation	1.28	1.55
Sample Variance	1.64	2.39
Kurtosis	-0.43	-1.46
Skewness	0.33	0.07
Range	4.82	4.38
Minimum	3.70	3.92
Maximum	8.52	8.30
No of compounds	28.00	12.00

Table 7: t-Test: Two-Sample Assuming Unequal Variances

	BRD4 (BD1) activity	Predicted activity
Mean	5.86	5.84
Variance	1.82	1.78
Observations	40.00	40.00
Hypothesized Mean Difference	0.00	
df	78.00	
t Stat	0.07	
P(T<=t) one-tail	0.47	
t Critical one-tail	1.66	
P(T<=t) two-tail	0.95	
t Critical two-tail	1.99	

Table 8: Y-Randomization test for the training set

Model	R	R^2	Q^2
Original	0.96	0.93	0.70
Random 1	0.41	0.17	-1.44
Random 2	0.52	0.27	0.02
Random 3	0.43	0.19	-0.11
Random 4	0.18	0.03	-0.34
Random 5	0.42	0.17	-0.36
Random 6	0.27	0.07	-0.38
Random 7	0.43	0.19	-0.83
Random 8	0.30	0.09	-0.53
Random 9	0.56	0.31	-0.58
Random 10	0.42	0.18	-0.58
Random Models Parameters			
Average r :	0.39		
Average r^2 :	0.17		
Average Q^2 :	-0.51		
cRp^2 :	0.85		

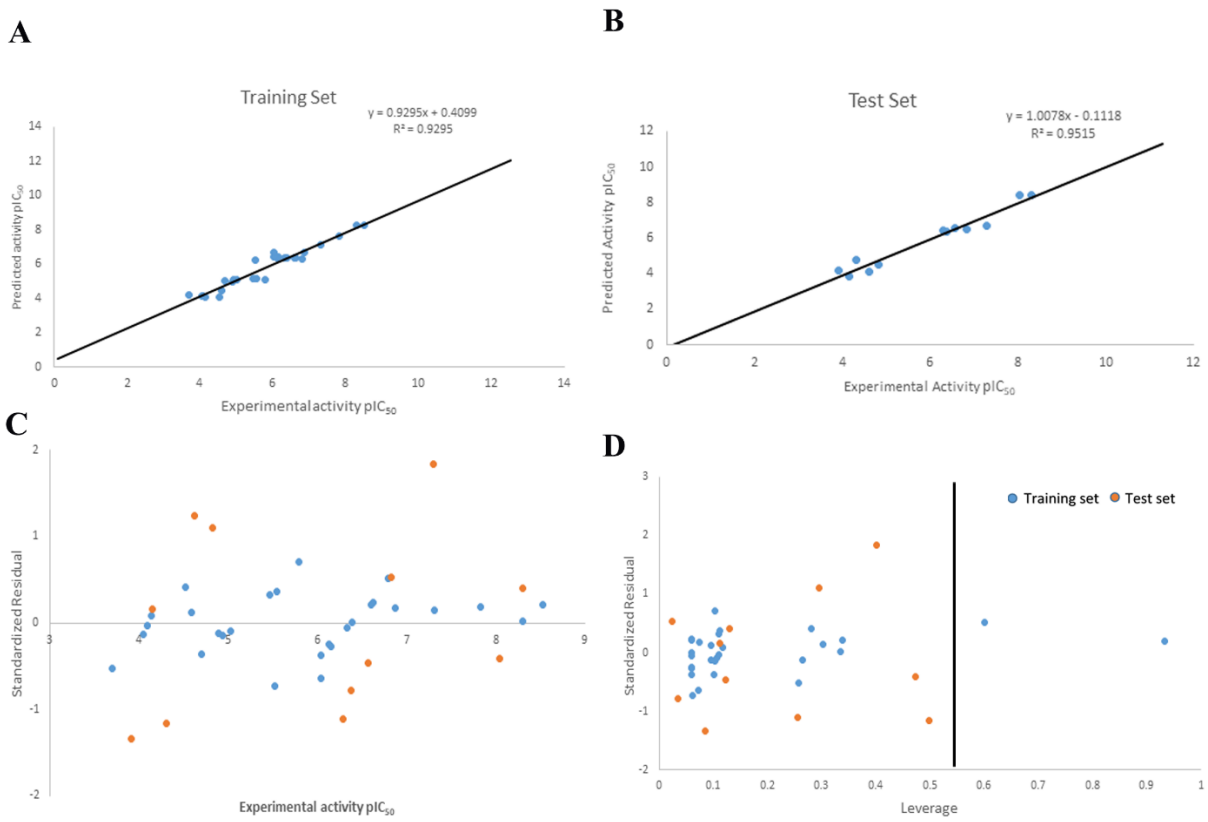
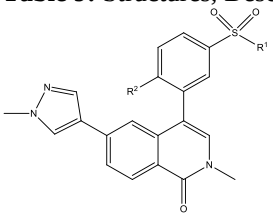


Fig. 1: (A) Plot of predicted activity against experimental activity of training set. (B) Plot of predicted activity against experimental activity of test set. (C) Plot of standardized residual against experimental activity pIC_{50}. (D) Williams Plot of standardized residual activity against leverages.

Table 9: Structures, Descriptors and predicted pIC_{50} (µM) of novel compounds



S/No	R^1	R^2	BCUTp-1l	nBondsD2	ndssC	ma xssO	pIC_{50}
1	Et	nBu	5.15	4	2	6.09	8.26
2	Me	nPt	5.13	4	2	6.12	8.22
3	Et	Iso-Bt	5.46	4	2	6.11	9.23
4	Et	Iso-Pt	5.46	12	9	6.20	8.24
5	Et	Diiso-Pr	5.47	12	9	6.27	8.28

Discussion

In this study, Material studio 2017 software employed Genetic Function Approximation (GFA) method to generate four different models. Due to statistical significance which satisfies the recommended standard for a reliable and stable model shown in **Table 2**, the first model was selected to be the best model.

Table 4 shows 2D descriptors are vital in predicting the activity of new molecules that can inhibit BRD4-BD1. The negative coefficient of the descriptors in

model 1 inferred that the pIC_{50} of the compounds that fall between the warning limit of the William's plot decreases as the value of the descriptor increases. Conversely, the positive coefficient of the descriptors in model 1 inferred that the pIC_{50} of the compounds that fall between the warning limit of the William's plot increases as the value of the descriptor decreases. Therefore, to design a potent compound with high pIC_{50} value, negative coefficient of the descriptor has to reduce while the positive coefficient has to increase. The Pearson's correlations of the descriptors presented in **Table 5** shows a correlation between ndssC descriptor and nBondsD2 descriptor with a value of 0.70 while the low correlation values ≤ 0.5 in other descriptors inferred that most of the descriptors do not correlate with one another.

The descriptive statistics of the inhibition data for both training set and test set shown in **table 5** inferred that the value of the training set range from (3.70- 8.52) while the value of the test set range from (3.92- 8.30). Also, the mean value of the training set (5.82) and the mean of the test set (5.96) affirmed that the data sets were randomly divided to give a reliable means for validating the built model internally and externally. The model is further validated to check if there is significant difference in the mean of the activities (experimental and predicted). **Table 7** gives the summary of t-Test: Two-Sample Assuming Unequal Variances analysis at p=0.05. The report inferred that at 95% confidence limit, there is no significance difference between the mean of the experimental and predicted activity.

In order to accept that the model gotten from Genetic Function Approximation (GFA) method is not by chance, Y- Randomization test is done which is presented in **Table 8**. The low value of R^2, Q^2 for several trials and cRp^2 (0.85 ≥ 0.5) ascertain that the model built is not by chance and it is reliable to predict the activity of a new molecule.

The coefficient of determination R^2 for both training set and test is reported in **Figure 1A & 1B**. The high value of R^2 shown on the plot confirmed that the model can successfully predict the activity of a new compound due to its correlation with the experimental activity.

The randomness of the activities on both negative and positive sides of y-axis shown on the scatter plot between Standardized Residual activity and the experimental activity reported in **Figure 1C** confirms the built model is free from systematic error.

To discover influential and outliers compounds in the built model, the standardized residual activity for the entire data set was plotted against the leverages. The plot (Williams plot) confirms the presence of two influential compounds (22 and 35) which are both from the training set. The two compounds are deemed influential because the leverage value is higher than the warning value (h= 0.54).

Based on the built model, five novel compounds of ethyl sulfone analogs were designed which was showed in **Table 9** to have good predicted bioactivity. Hence, these compounds may be considered as good candidates for further experimental analysis.

Conclusion

QSAR study on a novel Substituted 4-Phenylisoquinolinones was carried out using GFA method. The built model was validated internally using the training set and externally using the test set and the validation parameters were detected to be in cordial agreement with the recommended standard for an acceptable QSAR model. The built model was used to predict the activity of five novel compounds as BET bromodomain inhibitors. The four descriptors employed to build the model are BCUTp-1l, nBondsD2, ndssC and maxssO. The study shows that more potent compounds with Substituted 4-Phenylisoquinolinone as the lead compound can be designed and synthesised as BRD4-BD1 inhibitors.

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