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QSAR Study of N-((3-Benzamido-4-oxo-3,4-Dihydroquinazolin 2-yl) methyl)-N-(Substituted) Phenyl Benzamide as Antiulcer Agents

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ABSTRACT

Suppression of gastric acid secretion by use of proton pump inhibitors is an efficient way to control hyperacidity complications. An inhibitory activity of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides on H+/K+-ATPase was established and reported earlier. Thus, it is significant to develop more promising agents by quantitative structure-activity relationship (QSAR) study of 37 ligands by multi-linear regression method to link the structures of molecules with inhibitory activity on H+/K+-ATPase (pIc50). QSAR model was built using genetic function approximation protocol of the software Discovery Studio Version 2.1 using training set carrying 23 compounds. The remaining 14 compounds were used as a test set. The generated model was showing satisfying statistical qualities, r2=0.84 and predicted correlation coefficient r2pred=0.88. The theoretical approach indicates that an increase in Log D, Shadow_XZ and SC 2, and reduction of Shadow_Z length causes more inhibition of enzyme by molecule.

KEYWORDS

Antisecretory Agents, Antiulcer Activity, H+/K+-ATPase, H+/K+-ATPase Inhibitors, QSAR, Quinazolines

INTRODUCTION

Maximum people worldwide experience acidity occasionally. The prevalence of hyperacidity is increasing day by day due to multiple factors like, frequent use of Nonsteroidal anti-inflammatory drugs, by H-pylori infection, life style and daily habits of the people, which include eating high amount of meal and lying down after taking meal, food with high fat amount, types of food that can tend to increases acidity in stomach, family history of GERD, drinks like alcohol, smoking, high body mass index (BMI), less physical activity and age (Matsuura et al., 2013; Ter et al., 1998). The continuous experience of acidity symptoms on a regular basis can produce countable effects on quality of life (Dean et al., 2004; Tack et

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al., 2012; Pilotto et al., 2016; Maekawa et al., 1998). Additionally Gastric hyperacidity eventually may precipitates into Gastroesophageal reflux disease (GERD) (Craven et al., 2018, Johnson et al., 2004). It is a state of gastric hyperacidity where acid content from the stomach reverse back into the esophagus (Ness-Jensen et al., 2012). If GERD is left untreated, it may lead to life-threatening complications, like peptic ulcer, perforation and bleeding of GIT due to ulcer, Failure of esophageal peristalsis (Achem. Et al, 2003) and laryngopharyngeal carcinoma (Jarosz et al., 2014;). The worldwide prevalence of GERD is about 8.8–25.9% in Europe, 18.1–27.8% in North America, 11.6% in Australia, 8.7–33.1% in the Middle East, 2.5–7.8% in East Asia and 23.0% in South America (El-Serag et al., 2014, Mahadeva et al., 2005; Eusebi et al., 2018). Simultaneously, there is also an increase in economic burden of health care system by rise in prevalence of the GERD and other complications (Becher et al., 2011). In most of such cases of gastric hyperacidity, people are not consulting with health care provider, but there are the cases were people are needed to be hospitalized as well as have to go though invasive surgeries when there are complications due to high GIT (Gastrointestinal system) damage (Thukkani et al., 2010; Sonnenberg et al., 1994). Despite of high research and discovery of different class of new drugs till date in this area, there is no promising agent to deal with the chronic hyper gastric acidity, GERD and Gastric ulcer (Vaezi et al., 2017; Fass et al., 2001). The drugs like antacids and other present antisecretory agents can deal with Hyperacidity and neutralize it or decrease the acid secretion. But even though people are getting temporary relief from the symptoms on taking available drugs and relapse of acidity is frequently seen in many cases. Therefore the permanent solution is needed to be searched to address this situation. In addition, many patients are required to take medicines for longer time to deal with gastric disturbance generated by treatment of different types of cancers or while undergoing long term treatment of some infections like Tuberculosis. So, drug induced Hyperacidity is also the matter of concern.

As a part of our affords to improve the quality of life of people suffering from gasric hyperacidity and to prevent other complications, in our earlier work, We have synthesized and reported the Antisecretory activity of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides by inhibition of H^+/K^+ ATPase. The activity was measured by an in-vitro method using an isolated Hog gastric H^+ /K^+ -ATPase enzyme. All the compounds were found to be potent inhibitors of Isolated Hog stomach H^+ / K^+-ATPase enzyme with variant efficacy (parmar, 2014;Parmar & suhagia, 2021). It is significant to discover new molecules of the same series with high inhibitory action on H^+ /K^+ -ATPase enzyme with the help of QSAR (Quantitative Structure Activity Relationship) (Kenard et al., 1969; Bhadoriya et al., 2015; Hansch et al., 2004).

In continuation of our affords, in this present work we are proposing QSAR model which can be used to get more efficient agents of the series of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides. QSAR remains an efficient method for building mathematical models to search out a statistically significant correlation between the chemical structure and continuous (pIC_{50}, pEC_{50}, Ki, etc.) or categorical/binary (active, inactive, toxic, nontoxic, etc.) toxicological/biological property using classification and regression techniques, respectively (Eriksson et al., 2003; Hernandez et al., 2009; Worachartcheewan et al., 2014, Hanch et al., 1995). QSAR methods are important tool for prediction of biological effect of chemical compounds based on mathematical and statistical relations (Hansch et., 1964; Hansch et., 2004; Chtita et al., 2016, Abraham et al., 2000). QSAR being one of the Computer added drug design (CADD) method which can help to find out more active and novel agent of known series of molecules that can be synthesized and screened subsequently (Sabet et al., 2010; Chen et al., 2015; Zhang et al., 2011). Here, we present a quantitative structure–activity relationship (QSAR) study of 37 legands to rationalize the relationship between the structural and physicochemical features of a series of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin-2-yl) methyl)-N-(substituted phenyl) benzamide with biological activity, which would help to discover more efficient and promising Antiulcer agents. (Talele et al., 2010)

Moreover, it was reported earlier in QSAR study of schiff bases of quinazolinones as H^+ /K^+ ATP-ase inhibitors, it was proposed that compounds must have high value of polar surface area, hydrophobic constant, and polarizablity. These properties was playing crucial role in the activity of the designed

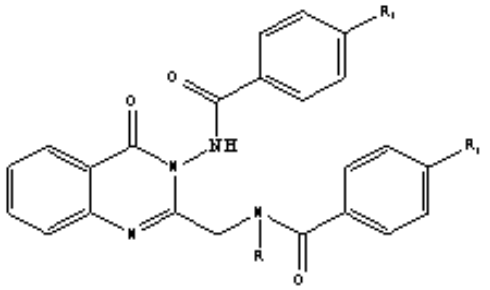
Quinazoline derivatives compounds.(Jaiswal et al., 2021) In Quantitative structure-activity relationship and molecular modeling study on a series of Heteroaryl- and heterocyclyl-substituted imidazo[1,2-a] pyridine derivatives acting as acid pump antagonists, It was proposed that the derivatives may inhibit the enzyme through some electronic interaction with the enzyme and some of their small substituents may participate in hydrophobic interaction as well as steric interactions. (Agrawal et al., 2018). The quantitative structure-affinity relationship (QSAR) of other 30 quinazolinone derivatives as H^+/K^+-ATPase inhibitors showed that polarizablity and stearic properties of molecues are important for activity. (Mahmmad et al., 2018). These QSAR studies are not showing the role of these descriptors in mechanism of Potassium competitive acid blocker and how can it accelerates inhibition of enzyme. In proposed QSAR we also correlate the role of influencing descriptor in mechanism of biological action of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin-2-yl) methyl)-N-(substituted phenyl) benzamide derivatives.

METHODS AND MATERIAL

Experimental Data

Selection of Training and Test Sets

To construct QSAR model of N-((3-Benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-N-(substituted) phenyl benzamide analogs, out of 37 molecules, 23 representative molecules were sorted as a training set (Golbraikh et al., 2003; Shahlaei et al., 2013). The remaining 14 compounds were used as a test set molecules. The structures of 23 compounds of training set and their antiulcer activity are shown in Table 1. For every compound, the experimental values of biological activity were used in the negative logarithmic scale (pIC_{50}) to achieve normal distribution. For QSAR study, all compounds' structures were sketched by using Visualizer module of Discovery studio 2.1 software (Accelrys Inc., USA). To calculate potential energy CHARMM force field was used (Platts et al., 1999). All the compounds were energy minimized by using Smart Minimizer method until the root mean square gradient value becomes smaller than 0.001 kcal/mol Å, followed by geometry optimization by semi empirical MOPAC-AM1 method (Astin Method-1) (Parac et al., 2003).



Descriptors Selection

Numerous physicochemical descriptors involving structural, thermodynamic, steric, electronic and quantum mechanical descriptors, were calculated by calculate molecular properties protocol of the software Discovery Studio ver. 2.1. The descriptors which are showing intra correlation value of 0.9 or above in correlation matrix were highly correlated descriptors and were removed from the study. The remaining descriptors were used for QSAR models. QSAR models were built using descriptors showing no inter correlated along with lesser degree of multi-co-linearity (Tropsha et al., 2010). VIF (Variance of Inflation) value was obtained by equation $1/1\text{-}r^2$ and r^2 was the multiple correlation coefficient of one descriptor's effect regressed on the remaining molecular descriptors and it is indicated in Table 3. Values of Variance inflation factor (VIF) were also less than 10 which describes that the descriptors were not inter-correlated (Veerasamy et al., 2011). The correlation values of selected descriptors are given in Table 2. The value of selected descriptors for each molecule is given in Table 4.

Table 1.
Training set compounds

Sr. No.	Compound	R	R_1	IC_{50}	PIC_{50}
1.	LMDP-2	4-Methylphenyl	H	12	4.92081
2.	LMDP-3	3-Methylphenyl	H	15	4.74472
3.	LMDP-4	4-Methoxylphenyl	H	22	5.1549
4.	LMDP-5	3-Methoxylphenyl	H	8	5.008712
5.	LMDP-6	2-Methoxylphenyl	H	9	4.677781
6.	LMDP-7	4-Chlorophenyl	H	13	4.85387
7.	LMDP-8	2-chlorophenyl	H	15	4.958607
8.	LMDP-9	3-Chlorophenyl	H	13	4.619789
9.	LMDP-10	4-Fluorophenyl	H	13	4.257577
10.	LMDP-11	4-Trifluoro methyphenyl	H	15	3.721246
11.	LMDP-13	3-Chloro,4-fluoro phenyl	H	20	3.853872
12.	LMDP-14	2,3 Dichlorophenyl	H	22	3.619789
13.	LMDP-16	3,4 Dichlorophenyl	H	11	3.9415
14.	LMDP-19	2,4 Dichlorophenyl	H	18	4.619789
15.	LMDP-21	Phenylethyl	H	9	4.92081
16.	LMDP-22	2,4 Dimethylphenyl	H	13	4.74472
17.	LMDP-23	3,6 Dimethylphenyl	H	8	5.1549
18.	LMDP-25	2,5 Dichlorophenyl	H	10	5.008712
19.	LMDP-26	5-Chloro 2-methyl Phenyl	H	25	4.677781
20.	LMDP-27	5-Bromo 2-methyl Phenyl	H	23	4.85387
21.	LMDP-28	4-Bromophenyl	H	22	4.958607
22.	LMDP-29	4-Nitrophenyl	H	19	4.619789
23.	LMDP-30N	Phenyl	H	14	4.257577

In Compounds, LMCP-1 to LMCP-29, R_1= H, in Compound, LMCP-30N, R_1= NO_2

Table 2.
Correlation matrix of descriptors used in the generated models

Property	Log D	Shadow_Z length	Shadow_XZ	SC 2
Log D	1			
Shadow_Z length	0.039293	1		
Shadow_XZ	0.480702	0.101936	1	
SC 2	-0.25524	0.474559	-0.24798	1

Table 3. VIF values of descriptors

Sr. No.	Descriptor	VIF
1	Log D	1.07
2	Shadow_Z length	1.33
3	Shadow_XZ	1.28
4	SC 2	1.21

Table 4.
Value of selected descriptors

Sr.No	Comp. No.	Shadow_XZ	LogD	Shadow_Z length	SC_2
1	LMDP-1	340.90	62.337	14.744	24.907
2	LMDP-2	425.38	58.216	18.772	25.07
3	LMDP-3	438.51	64.281	16.923	25.877
4	LMDP-4	386.83	64.957	16.039	25.587
5	LMDP-5	405.97	63.815	16.768	25.457
6	LMDP-6	411.81	63.971	13.56	25.614
7	LMDP-7	429.04	70.095	13.881	26.648
8	LMDP-8	437.45	60.372	16.782	25.777
9	LMDP-9	452.08	75.88	13.989	28.277
10	LMDP-10	461.55	73.628	17.216	28.277
11	LMDP-11	414.41	68.526	14.91	26.485
12	LMDP-12	457.90	67.469	13.371	26.485
13	LMDP-13	471.03	61.484	13.449	26.485
14	LMDP-14	438.48	97.507	15.788	27.355
15	LMDP-15	378.39	61.846	17.773	25.3567
16	LMDP-16	446.93	62.141	16.317	25.237
17	LMDP-17	382.28	60.484	16.298	26.321
18	LMDP-18	405.36	67.434	14.346	26.648
19	LMDP-19	414.83	64.741	15.884	26.648
20	LMDP-20	401.70	64.397	15.304	26.648
21	LMDP-21	415.71	68.7	16.22	26.648
22	LMDP-22	413.77	61.398	16.524	26.648
23	LMDP-23	390.73	59.91	16.761	26.648
24	LMDP-24	329.20	68.32	18.098	26.648
25	LMDP-25	360.32	64.604	15.724	25.777
26	LMDP-26	352.28	60.189	16.305	26.648
27	LMDP-27	363.97	134.271	16.92	29.802
28	LMDP-28	401.46	62.337	14.127	24.907
29	LMDP-29	348.62	58.216	14.483	25.07
30	LMDP-30 33333339933333030N	375.32	64.281	16.042	25.777
31	LMDP-31N	361.75	64.957	14.744	25.777
32	LMDP-32N	372.42	63.815	18.772	25.777
33	LMDP-33N	360.69	63.971	16.923	25.614
34	LMDP-34N	337.65	70.095	16.039	26.648
35	LMDP-35N	409.87	60.372	16.768	25.777
36	LMDP-36N	362.63	75.88	13.56	28.277
37	LMDP-37N	375.32	73.628	13.881	28.277

Generation of QSAR models

QSAR model were constructed using Genetic Function Approximation protocol of the software Discovery Studio Version 2.1. To judge Statistical qualities of the generated models, the validation parameters (Cramer et al., 1988, Friedman et al., 1991) such as regression coefficient (r^2), *adjusted* r^2 *(*r^2*adj)*, *cross-validated* r^2 *(*r^2*cv)*, *F-value*, and *Friedman's LOF* were calculated and embedded already in the software. The equation's length was fixed up to five terms, more over the size of population was set as 100, the probability of mutation was framed as 0.1 and simple fully quadratic terms and linear polynomial equation term was adjusted (Jitender et al., 2010). Initially, 100 QSAR equations were generated that consist of 4 descriptors among QSAR random models. The best selected equation with the satisfactory value of statistical parameters is given below and statistical values are described in Table 5.

pIC_{50}= 2.61029+ 0.0335472 * Shadow_XZ+ 0.37837 * <LogD − 4.95365>− 1.45268* <Shadow_Zlength − 6.38908>+ 0.0915749 * <60.138 − SC_2>

RESULTS AND DISCUSSION

Validation of Model

To validate the model is one of the most crucial aspect of QSAR analysis. It is the process by which the predictive capacity of a QSAR and the mechanistic basis can be assessed in favour of practical purpose (Wold et al., 1991). Two methods of Validation can be used to determine integrity of the generated models, internal validation and external validation. (Roy et al., 2016, Tropsha et al., 2003)

Internal Validation

For internal validation the dataset used was from which the model was generated (Veerasamy et al., 2011). Here, Cross-Validation methods were used as internal validation method which includes Leave-one-out, Leave-Many-Out and Leave-Some-Out. The correlation coefficient of the cross-validation procedure, r^2 *cv* (Cross validated R square) was determined to check quality of the model which was found to be 0.77. The generally accepted value for an adequate QSAR model is $r^2cv > 0.5$ (Tropsha et al., 2010, Hernandez et al., 2009). In another way validation was carried out by determining residuals of observed and predicted biological activity of training set. It was seen that the predicted activity

Table 5.
Statistical values of generated QSAR Model

Statistical parameters	Value
R-squared (r^2)	0.84060
Adjusted R-squared (r^2adj)	0.8026
Cross validated R-squared(r^2cv)	0.7714
Friedman LOF	0.03414
Significance-of-regression F-value	22.1496
Minimum experimental error for non-significant LOF (95%)	0.06936
r^2pred	0.88
r^2ext	0.81

and actual activity of training was very near and residuals value was very less. The actual activity, predicted activity and residuals for training set compounds are indicated in Table 6 and the graphical presentation showing linear relationship actual and predicted activity as shown in Figure 1.

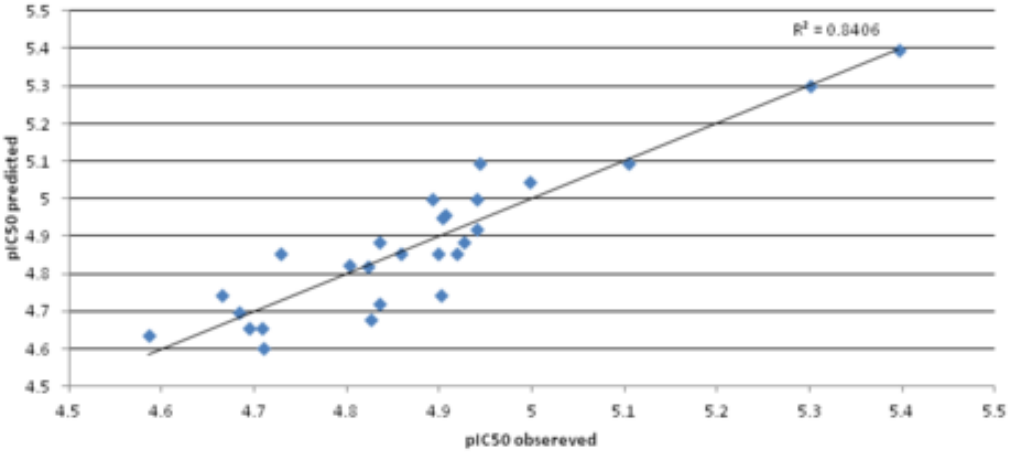
External Cross-Validation

Even if model is with excellent statistical characteristics (like r^2, r^2 *cv, F-value*) and having satisfactory predictions, it is seen that sometimes there is a lack of true relationship between molecular descriptors and target property (Konovalov et al., 2008). Therefore, a reliable validation procedure must be carried out to avoid chance correlation. The validation of the model by external validation and determination of validation parameter like predictive r^2 *(*r^2*pred)* value of test set compounds (Roy, 2016) is ultimate method to establish integrity of any QSAR model. In external validation, the quality of QSAR model is mostly checked by determining its ability to perform predictions of compounds' activity those are not included in the training sets. In this regard,the activity of Test set compounds were predicted and the real validation of QSAR model was accomplished by determining and examining residuals of actual and predicted activity of Test compounds. The actual activity, predicted activity and residuals for test set compounds are tabulated in Table 7 and represented as Figure 2. It is showing that the predicted

Table 6.
Results of the internal validation study

Sr. No.	Compound	Observed Activity (pIC_{50})	Predicted Activity (pIC_{50})	Residuals
1	LMDP-2	4.823	4.82	0
2	LMDP-3	5.301	5.301	0.051
3	LMDP-4	4.708	4.657	0.114
4	LMDP-5	4.899	4.853	0.046
5	LMDP-6	4.859	4.853	0.006
6	LMDP-7	4.694	4.657	0.037
7	LMDP-8	4.728	4.853	-0.125
8	LMDP-9	4.919	4.853	0.066
9	LMDP-10	4.803	4.823	-0.02
10	LMDP-11	4.892	5	-0.108
11	LMDP-13	4.728	4.853	0.108
12	LMDP-14	4.919	4.853	-0.052
13	LMDP-16	4.803	4.823	0.04
14	LMDP-19	5.092	5	-0.015
15	LMDP-21	4.803	4.823	-0.001
16	LMDP-22	5.092	5	0.021
17	LMDP-23	4.823	4.82	0
18	LMDP-25	5.301	5.301	0.051
19	LMDP-26	4.708	4.657	0.114
20	LMDP-27	4.899	4.853	0.046
21	LMDP-28	4.859	4.853	0.006
22	LMDP-29	4.694	4.657	0.037
23	LMDP-30N	4.728	4.853	-0.125

Figure 1.
Scatter plot of observed vs. predicted pIC_{50} for training set (Internal validation)



activity of test set compounds was appear to be very near to their actual activity as shown, which is showing the high robustness of model. But the residual observation is not only the optimum criteria for validation of the model. Hence, additionally the external predictability of the model was assessed by deriving r^2pred value for the given model (Roy et al., 2009). *r^2pred* is the predicted correlation coefficient and it is calculated from the predicted activity of all the test set compounds by equation

$$r^2\text{pred} = 1 - \frac{\Sigma (\text{YPred(test)} - \text{YObs(test)})^2}{\Sigma (\text{YObs(test)} - \text{Y}(\bar{y}\text{training})^2}$$

Where, *YPred(test)* and *YObs(test)* were the predicted and observed activity values, respectively, of the test set compounds and $\bar{Y}$training was the mean activity value of the training set. Again the value of r^2pred was came out as greater than 0.5 (0.88) and so indicating good external predictability (Hernandez et al., 2009). Further, the value of rm^2 (Roy, et al., 2009; Roy, et al., 2012) is also a promising measure of evaluation of the predictive power of the QSAR model which may be determined by equation

$$rm^2 = r^2\left(1 - \left| Ö(r^2 - r_0^2) \right|\right)$$

Where r^2 is the squared correlation coefficient between predicted and observed values and rm^2 was the squared correlation coefficient between predicted and observed values without intercept. As the r^2m value was found to be greater than 0.5 (0.75), good external predictability can be achieved. The Model is observed to be the best based on internal and external predictability, by values *of r^2, LOF, r^2cv, F-value, r^2pred, r^2m* values 0.9146, 0.100, 0.865, 41.09, 0.88, 0.75 respectively (Roy et al., 2012).

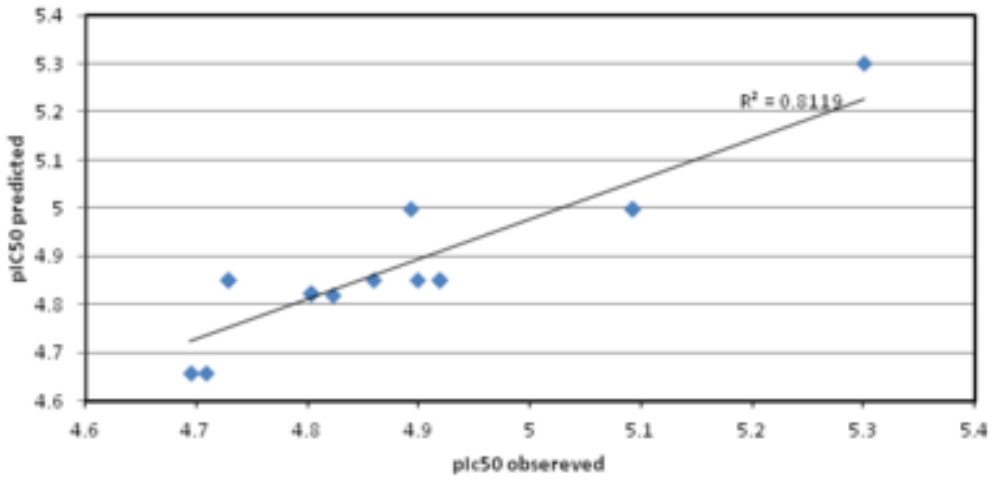
Discussion of Qsar Study

QSAR techniques was successfully applied on N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides as an inhibitor of H^+/K^+ATPase in order to produce a model that relates the chemical structures of the molecules with their inhibitory activity on enzyme. A reliable, predictable and robust model was generated by Genetic Function Approximation (GFA) technique in Discovery Studio software version 2.1. In this work, we have screened 21 preselected

Table 7.
Results of the external validation study

Sr.No.	Comp. No.	Observed activity	Predicted Activity	Residuals
1	LMDP-1	4.82	4.92081	-0.10081
2	LMDP-12	5.301	4.74472	0.55628
3	LMDP-15	4.657	5.1549	-0.4979
4	LMDP-17	4.721	5.008712	-0.28771
5	LMDP-18	4.853	4.677781	0.175219
6	LMDP-20	4.853	4.85387	-0.00087
7	LMDP-24	4.657	4.958607	-0.30161
8	LMDP-31	4.853	4.619789	0.233211
9	LMDP-32	4.853	4.257577	0.595423
10	LMDP-33	4.823	3.721246	1.101754
11	LMDP-34	5	3.853872	1.146128
12	LMDP-35	4.602	3.619789	0.982211
13	LMDP-36	4.638	3.9415	0.6965
14	LMDP-37	4.886	4.619789	0.266211

Figure 2.
Scatter plot of observed vs. predicted pIC_{50} for test set (External validation)



descriptors of synthesized molecules to correlate with activity of inhibition of H^+/K^+ ATPase enzyme. Out of these 21 descriptors, 4 descriptors were showing least inter correlation, and they were used to generate the QSAR model. Initially, 100 QSAR equations were produced carrying different statistical values. However, finally the best model was selected which was showing acceptable statistics to rationalize the alliance between properties of molecules and activity. It is important to carry out validation of model. To validate the model the internal and external validation was performed. The

value of validation coefficient of internal and external validation R^2 was found to be 0.9553 and 0.9894 respectively. The models displayed satisfactory r^2pred and rm^2 values also The generated model shows that the H^+/K^+ATPase inhibitory activity of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides is influence by descriptors like Log D, Shadow_Z length, Shadow_X Z and SC 2 descriptors with greatest extend.

The theoretical approach suggests that an increase in distribution coefficient (logD) has positive influence on the biological activity. Log D is simply being calculated from predicted Log P and predicted pKa of singly ionized species at certain pH. Incresed in LogD value can cause increase in biological activity. It reveals that the drug should be ionized at gastric pH in enough amount and also shld carry lipophilicity to avail at the site of action to bind with enzyme in luminal area of GIT (Gastrointestinal tract). Beyond this, the geometric characteristic also plays major role in augmentation of biological activity of molecules of described series. Geometric descriptor like Shadow XZ length is important for biological action, incrase the value of shadow XZ length give rise to biological action. Shadow XZ length is important for shape analysis of molecules. There is Positive contribution of Shadow XZ length towards biological activity. Shadow indices are set of geometric descriptors to characterize the shape of the molecules (Rohrbaugh et al., 1987). These descritors are calculated by projecting the model surface of molecule on three mutually per pendicular planes: xy, yz and xz. The molecules are first rotate to align the principle moment of intertia with x, y and z axes. They are not only depended on conformation of molecule but also on orientation of molecule. According to equation, principal moment of Shadow_Zlength is principal descriptor contributing negatively on biological activity of the compounds. So low value of Shadow_Zlength ause improvement in biogical action. Additionally increase in topological descriptor SC_2 also gives beneficial effect in biological response. (Chtita et al., 2014). These geometric descriptors allows three dimension binding of drug with enzyme in proper way to produce desired biological action.

$$pIC_{50} = 2.61029 + 0.0335472 * \text{Shadow\_XZ} + 0.37837 * \langle \text{Log D} - 4.95365 \rangle - 1.45268 * \langle \text{Shadow\_Zlength} - 6.38908 \rangle + 0.0915749 * \langle 60.138 - \text{SC\_2} \rangle$$

The Acid pump antagonists' mechanism of action suggest that these agents undergoes protonation in gastric pH and the protonated form of molecule bind with H+/K+ ATPase reversibly instead of Potassium and inhibits the enzyme for a period of time. The QSAR study indicates that if lipophilic and electronic factor is increased that may increase inhibition of enzyme. More electronic property by adding electronic releasing groups facilitates the protonation of molecule and more lipophilicity by alkyl or aromatic substitution will avail the molecule at luminal site of stomach for its action. The geometric parameter also facilitates the binding of molecule with enzyme.

Proposed Novel Compounds

Based on QSAR model correlation between biological activity and Molecular property new molecules can be designed and suggested which are supposed to be more promising compare to existing molecules. As indicated by model, the novel molecule should carry functional group (amines) that ionized at acidic pH of gastric juice with satisfactory pKa value and simultaneously enough lipophilic to gain desired log D value. The role of Geometric descriptors and topological descriptors suggest that molecular geometry is equally important for biological action. Increasing topological descriptor in particular bond and ring may have promising effect on activity

CONCLUSION

In developed QSAR model, a strong correlation was observed between the experimental and predicted values of the biological activities and It is showcasing the validity and quality of the QSAR model.

The Model is observed to be the best based on internal and external predictability, by values *of* r^2, *LOF,* r^2*cv, F-value,* r^2*pred,* r^2*m* values 0.9146, 0.100, 0.865, 41.09, 0.88, 0.75 respectively. As the r^2m value was found to be greater than 0.5 (0.75), good external predictability can be achieved. The relatively high values of predicted correlation coefficient r^2pred = o.88, reveals predictive potential of a QSAR model. The model is capable to predict biological activity of new untested compounds. The most important finding from this research is that we have been able to design and predict new compounds with higher or lower values than existing compounds by adding suitable substitutions and by calculating their propriety. Thus, we conclude that the proposed models will reduce the time, the cost, and also the human mobilization.

AUTHORS' CONTRIBUTIONS

Dr. D. R. Parmar has established the QSAR models and prepared the manuscript. Dr. B. N. Suhagia participated in the drafting QSAR and has revised the manuscript. Both authors read thoroughly and approved the manuscript for publication.

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CONFLICT OF INTERESTS

None of the authors have conflicting ideas, research, beliefs, etc.

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