QSAR and docking studies of 3, 5-dimethylpyrazole as potent inhibitors of Phosphodiesterase-4

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Abstract

A quantitative structure-activity relationship (QSAR) study was performed to develop a model on a series of 3, 5-dimethylpyrazole containing furan moiety derivatives which exhibited considerable inhibitory activity against PDE4B. The obtained model has correlation coefficient (r) of 0.934, squared correlation coefficient (r²) of 0.872, and leave-one-out (LOO) cross-validation coefficient (Q²) value of 0.733. The predictive power of the developed model was confirmed by the external validation which has (r²) value of 0.812. 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 (I-XV), results indicated that the compound III, V, XIII, and XV showed the strongest inhibition activity (IC50 = 0.2813, 0.5814, 0.6929, 0.6125μM, respectively) against PDE4B compared to the reference rolipram with (IC50=1.9μM).

Molecular docking was performed on a new designed compound with PDE4B protein (3o0j). Docking results showed that compounds (X and IX) have high docking affinity of -36.2037 and -35.2898 kcal/mol respectively.

Keywords: QSAR, molecular docking, pyrazole derivatives, PDE4 inhibitors, anti-inflammatory.

1. INTRODUCTION

Phosphodiesterase (PDE) are ubiquitous super family of enzymes that hydrolyze the phosphodiester bond and subsequent inactivation of second messenger molecules cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)1, they involved in the regulation of almost all physiological processes. In airway smooth muscle, inflammatory cell, and immune cells2, 3. The PDE enzymes consist of 11 families (PDE1 - PDE11) based on sequence homogeneity, inhibitor sensitivity, and biochemical properties4-6, they can be classified into three categories based on their substrate specificity. PDE4, PDE7, and PDE8 selectively hydrolyze cAMP7, whereas PDE5, PDE6, and PDE9 selectively hydrolyze cGMP. PDE1, PDE2, PDE3, PDE10, and PDE11 can hydrolyze both cAMP and cGMP with varying affinities, depending on the isoform8. Distributions of PDE enzymes in different cells and tissues together with their diversity and differences in enzymatic properties, allow individual isoforms to control specific physiological functions and link them to different pathological condition. Subsequently, selective PDE inhibitors have the potential to provide therapeutic benefit in the field of inflammation, cognition, lipogenesis, proliferation, apoptosis, and differentiation9.

PDE4, the largest and one of the earliest discovered PDE families, encoded by 4 genes PDE4A, PDE4B, PDE4C, and PDE4D each one of them has different function10, 11, play a key role in the hydrolysis of cAMP, which can selectively catalyze the hydrolysis of a 3-phosphodiester bond, forming an inactive 5-monophosphate12, 13. PDE4 isoforms expression is ubiquitous. PDE4A is highly expressed in brain, cardiovascular tissues, and small intestine cell14, 15, PDE4B and PDE4D highly expressed in immune cells16, 17, whereas PDE4C has been reported to be low expressed in the lung tissues. Inhibition of PDE4 considered to be a therapeutically potent in treatment of neurological, psychiatric disorder, respiratory and other inflammatory diseases in particular chronic obstructive pulmonary disorder (COPD) 18. Although a major therapeutic important of PDE4 inhibition, most of them have undesirable side effects, particularly nausea and emesis. Thus, it is important to understand the structural basis of PDE4 inhibitors, so that we can rationally design new molecules that minimize the undesirable side effects.
Quantitative structure–activity relationship (QSAR) is a method for building mathematical models, which attempts to find a statistically significant correlation between the chemical structure and biological/toxicological property using regression techniques. QSAR model is applied in drug discovery to produce a robust model, capable of determining toxicity or any desired biological effects of candidate compounds for new therapeutic molecules.\textsuperscript{19} QSAR modeling involves main steps: (i) Model building by collecting the data set compounds. (ii) Model validation with an internal validation using training set compounds to assess its quality. (iii) Model validation with an external validation using test set compounds to assess its predictability.\textsuperscript{20, 21}

The aim of this study is to develop a QSAR model to predict the activity of a new designed 3, 5-dimethyl-pyrazole derivatives (1-XV) as potent PDE4B inhibitors and to indicate the interaction between the inhibitor molecules and PDE4B protein (3o0j).

2. MATERIALS AND METHODS

2.1. QSAR studies

2.1.1 Data set

A set of 13 derivatives of 3, 5-dimethylpyrazole containing furan moiety as PDE-4 inhibitors reported by Hu et al.\textsuperscript{22} was used in the present study, their inhibition activity against PDE4B were expressed as (IC\textsubscript{50}) values half maximal inhibitory concentration. The (IC\textsubscript{50}) values were converted into the corresponding (pIC\textsubscript{50}) using the formula: pIC\textsubscript{50} = -log IC\textsubscript{50}, values and structures of the 3, 5-dimethylpyrazole derivatives are listed in Table 1.

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

2.1.2. Molecular descriptors generation

Molecular descriptors were calculated for each molecule after they subjected to energy minimization, these descriptors include 2D descriptors (e.g., log octanol/water partition coefficient, molecular weight, and number of H-bond acceptor atoms) and 3D descriptors (e.g., potential energy, ionization potential, highest occupied molecular orbital, lowest unoccupied molecular orbital, and density). In order to select the best subset of descriptors the ratio of molecules to the descriptors used is 5:1. The eight descriptors used to generate QSAR model denoted as potential energy (E), ionization potential (IP), highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), number of H-bond acceptor atoms (A-acc), density (D), molecular weight (MW), and log octanol/water partition coefficient (logP(o/w)) listed in Table 2.

Table 1: Biological activities and structures of 3,5-dimethylpyrazole derivatives\textsuperscript{22}

| Compound | R\textsuperscript{1} | IC\textsubscript{50} | pIC\textsubscript{50} |
|----------|----------------|----------------|----------------|
| 1        | 4-Cl           | 3.90           | 5.409          |
| 2        | 4-F            | 7.20           | 5.143          |
| 3        | 4-NO\textsubscript{2} | 15.40    | 4.812          |
| 4        | 4-CH\textsubscript{3} | 8.40     | 5.076          |
| 5        | 4-OC\textsubscript{H} \textsubscript{3} | 1.70      | 5.770          |
| 6        | 4-Br           | 51.10          | 4.292          |
| 7        | 3-Cl           | 20.90          | 4.680          |
| 8        | 3-F            | 20.20          | 4.695          |
| 9        | 3-NO\textsubscript{2} | 35.90    | 4.445          |
| 10       | 2-Cl           | 52.40          | 4.281          |
| 11       | 2-NO\textsubscript{2} | 62.70    | 4.203          |
| 12       | 2,4-di-F       | 3.20           | 5.495          |
| 13       | 2,6-di-F       | 14.50          | 4.839          |
| Rolipram | -               | 1.9            | 5.721          |

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

| Compd | E     | IP    | HOMO  | LUMO   | A-acc | D     | MW    | LogP(o/w) |
|-------|-------|-------|-------|--------|-------|-------|-------|-----------|
| 2     | 55.3429 | 8.9394 | -8.9394 | -1.0143 | 2.0000 | 1.0633 | 284.2900 | 3.0890    |
| 3     | 74.6415 | 9.5115 | -9.5115 | -1.6706 | 2.0000 | 1.0985 | 311.2970 | 2.8710    |
| 4     | 58.3698 | 8.7755 | -8.7755 | -0.8347 | 2.0000 | 0.9888 | 280.3270 | 3.2340    |
| 5     | 65.6616 | 8.6279 | -8.6279 | -0.8054 | 3.0000 | 1.0227 | 296.3260 | 2.8920    |
| 6     | 56.7612 | 9.0159 | -9.0159 | -1.0682 | 2.0000 | 1.1903 | 345.1960 | 3.7340    |
| 8     | 52.7089 | 9.0829 | -9.0829 | -1.0196 | 2.0000 | 1.0693 | 284.2900 | 3.1260    |
| 9     | 71.5365 | 9.4223 | -9.4223 | -1.3958 | 2.0000 | 1.1068 | 311.2970 | 2.9080    |
| 10    | 60.7120 | 9.0842 | -9.0842 | -0.8791 | 2.0000 | 1.0784 | 300.7450 | 3.5260    |
| 11    | 73.5499 | 9.4838 | -9.4838 | -1.2627 | 2.0000 | 1.1049 | 311.2970 | 2.8690    |
| 13    | 55.6333 | 9.0562 | -9.0562 | -1.0626 | 2.0000 | 1.1242 | 302.2800 | 3.2380    |
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 regressions (MLR) analysis was performed on the training set. Where calculated molecular descriptors served as the independent variable and the observed inhibition (pIC50) values were used as dependent variable. Several QSAR models were developed, the resulting QSAR model equation (1) showed a high regression coefficient. Values of regression coefficient and statistical parameters listed in Table 3.

\[ \text{pIC}_{50} = 21.82904 - 1.10399 \times \log P(o/w) + 1.49422 \times \text{HOMO} \]

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

|     | r  | r²  | Q²  | s    | F    | RMSE | P value |
|-----|----|-----|-----|------|------|------|---------|
|     | 0.934 | 0.872 | 0.733 | 0.185 | 54.640 | 0.165 | 0.000     |

Table 4: Experimental and predicted pIC50 for training set and cross validation against PDE4B.

| Compd | pIC50exp. | pIC50pred. | Residuals | CVpred. | Residuals |
|-------|-----------|------------|-----------|---------|-----------|
| 2     | 5.1430    | 5.0614     | 0.0816    | 5.0469  | 0.0961    |
| 3     | 4.8120    | 4.4472     | 0.3648    | 4.2546  | 0.5574    |
| 4     | 5.0760    | 5.1463     | -0.0703   | 5.1678  | -0.0918   |
| 5     | 5.7700    | 5.7443     | 0.0257    | 5.7017  | 0.0683    |
| 6     | 4.2920    | 4.2351     | 0.0569    | 4.1646  | 0.1274    |
| 8     | 4.6950    | 4.8062     | -0.1112   | 4.8188  | -0.1238   |
| 9     | 4.4450    | 4.5397     | -0.0947   | 4.5728  | -0.1278   |
| 10    | 4.2810    | 4.3626     | -0.0816   | 4.3973  | -0.1163   |
| 11    | 4.2030    | 4.4908     | -0.2878   | 4.6276  | -0.4246   |
| 13    | 4.8390    | 4.7223     | 0.1167    | 4.7078  | 0.1312    |

Table 5: Predicted pIC50 values of test set

| Compd | pIC50exp. | pIC50pred. | Residuals |
|-------|-----------|------------|-----------|
| 1     | 5.4090    | 4.5417     | 0.8673    |
| 7     | 4.6800    | 4.3644     | 0.3156    |
| 12    | 5.4950    | 4.7321     | 0.7629    |

2.1.4. Validation of QSAR model

To evaluate robustness of the model, internal validation was performed to the training set using leave-one-out (LOO) cross-validation method. The cross-validated regression coefficient (Q²) values were thereafter calculated according to the equation (1). External validation was performed in order to determine the predictive ability of the developed model by its application for prediction of test set values.

The observed activities and those calculated by QSAR model (Equation 1) for training set and test set were listed in Table 4 and 5.

2.1.5. Predict the activity of designed 3, 5-dimethyl-pyrazole derivatives (I-XV)

Chemical structures of the designed 3, 5-dimethyl-pyrazole derivatives (I-XV) were done using the ACD/ChemSketch, the developed QSAR model (Equation 1) was used to predict their inhibitory activity against PDE4B. The predicted activity expressed as pIC50 along with the structures listed in Table 6.
Table 6: Structures and predicted pIC\textsubscript{50} values for designed 3, 5-dimethylpyrazole derivatives against PDE4B.

![Chemical structure](image)

| Compd | R\textsuperscript{1} | R\textsuperscript{2} | pIC\textsubscript{50pred.} |
|-------|----------------|----------------|--------------------------|
| I     | H\textsubscript{2}NO\textsubscript{2}S- | -              | 5.4560                   |
| II    | H\textsubscript{2}NO\textsubscript{2}S- | Br             | 4.5091                   |
| III   | H\textsubscript{2}NO\textsubscript{2}S- | H\textsubscript{2}NO\textsubscript{2}S- | 6.5508                   |
| IV    | H\textsubscript{2}NO\textsubscript{2}S- | -              | 5.1826                   |
| V     | H\textsubscript{2}NO\textsubscript{2}S- | -              | 6.2355                   |
| VI    | H\textsubscript{2}NO\textsubscript{2}S- | -              | 3.9519                   |
| VII   | H\textsubscript{2}NO\textsubscript{2}S- | Br             | 3.0463                   |
| VIII  | H\textsubscript{2}NO\textsubscript{2}S- | H\textsubscript{2}NO\textsubscript{2}S- | 5.1352                   |
| IX    | H\textsubscript{2}NO\textsubscript{2}S- | -              | 3.6015                   |
| X     | H\textsubscript{2}NO\textsubscript{2}S- | -              | 4.7950                   |
| XI    | H\textsubscript{2}NO\textsubscript{2}S- | -              | 4.9759                   |
| XII   | H\textsubscript{2}NO\textsubscript{2}S- | Br             | 4.0290                   |
| XIII  | H\textsubscript{2}NO\textsubscript{2}S- | -              | 6.1593                   |
| XIV   | H\textsubscript{2}NO\textsubscript{2}S- | -              | 5.0846                   |
| XV    | H\textsubscript{2}NO\textsubscript{2}S- | -              | 6.2129                   |
2.2. Molecular docking

Docking simulation was conducted using MOE program. For this purpose, the structure of PDE4B was obtained from Protein Data Bank with PDB code 3o0j, structures of the new designed 3,5-dimethylpyrazole derivatives (I-XV) were built using ACD/ChemSketch v14.01 software 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.

Table 7: Binding scores and interactions of the docked designed 3, 5-dimethyl-pyrazole derivatives (I-XV) on the active site of 3o0j.

| Compd | S (kcal/mol) | Amino acid interaction | Type of interaction | Length (Å) |
|-------|--------------|------------------------|---------------------|------------|
| I     | -22.5848     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Glu304                 | Hydrogen bond       | 1.91       |
|       |              | His278                 | Hydrogen bond       | 3.04       |
| II    | -24.0097     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Glu304                 | Hydrogen bond       | 1.89       |
|       |              | His278                 | Hydrogen bond       | 2.92       |
|       |              | Phe446                 | Arene-Arene         | -          |
| III   | -25.5506     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Glu304                 | Hydrogen bond       | 1.84       |
|       |              | His278                 | Hydrogen bond       | 2.92       |
| IV    | -23.3100     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Tyr449                 | Arene-Arene         | -          |
| V     | -22.4087     | Phe446                 | Arene-Arene         | -          |
| VI    | -26.0465     | Asp275                 | Metal complex (Zn)  | 2.20       |
|       |              | Asp392                 | Metal complex (Zn)  | 2.18       |
|       |              | His238                 | Metal complex (Zn)  | 2.13       |
|       |              | His274                 | Metal complex (Zn)  | 2.21       |
|       |              | His234                 | Hydrogen bond       | 3.14       |
| VII   | -27.3758     | Asp275                 | Metal complex (Zn)  | 2.20       |
|       |              | Asp392                 | Metal complex (Zn)  | 2.18       |
|       |              | His238                 | Metal complex (Zn)  | 2.13       |
|       |              | His274                 | Metal complex (Zn)  | 2.21       |
|       |              | His234                 | Hydrogen bond       | 3.14       |
| VIII  | -21.0376     | His234                 | Hydrogen bond       | 2.87       |
|       |              | His234                 | Hydrogen bond       | 3.15       |
| IX    | -33.2888     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Glu304                 | Hydrogen bond       | 2.10       |
|       |              | Phe446                 | Arene-Arene         | -          |
| X     | -36.2037     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Glu304                 | Hydrogen bond       | 1.95       |
|       |              | Phe446                 | Arene-Arene         | -          |
| XI    | -8.9797      | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Phe446                 | Arene-Arene         | -          |
| XII   | -14.3970     | Asp275                 | Arene-cation (Mg)   | 2.08       |
| XIII  | -25.4920     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Glu304                 | Hydrogen bond       | 1.84       |
|       |              | His278                 | Hydrogen bond       | 2.94       |
| XIV   | -28.5605     | Asp275                 | Metal complex (Mg)  | 2.08       |
|       |              | Tyr449                 | Arene-Arene         | -          |
| XV    | -23.7545     | Phe414                 | Arene-Arene         | -          |

3. RESULTS AND DISCUSSION

3.1. QSAR studies

In the present work, structure activity relationship model was developed to correlate the structural features with biological response, the developed model showed squared correlation coefficient ($r^2=0.872$) which indicates the correlation between the inhibitory activity against PDE4B (dependent variable) the molecular descriptors (independent variable) for the training set data, and squared cross-validation ($Q^2=0.733$) which indicates that the newly developed QSAR model has a good prediction. Two molecular descriptors denoted as log octanol/water partition coefficient (logP (o/w)) and highest occupied molecular orbital (HOMO) were significantly correlated with the inhibitory activity. It is evident from the equation (1) that among the molecular descriptors, logP (o/w) is negatively correlated that means the biological activity decreases when the values of this descriptor are increased. On the other hand, the descriptor HOMO positively correlated, that mean the biological activity increases when the values of this descriptor are positively increased. Four compounds denoted by (test set) were used as external validation for developed QSAR model, and it was found that the predicted values through the QSAR model show compliance with their experimental values and ($r^2=0.812$), all statistical parameters calculated to evaluate the quality of the QSAR model were in suitable range.

Figure 1, 2, and 3 shows the correlation plots of the experimental versus predicted pK<sub>50</sub> values for training set, cross-validation and test set compounds against PDE4B respectively.
3.2. Docking study

Molecular docking study was performed between the target (PDE4B) and designed 3, 5-dimethyl-pyrazole derivatives (I-XV). All compounds were found to inhibit the receptor by occupying the active sites of the target (PDE4B). The binding affinity values for designed compounds range from -36.2037 to -8.9797 kcal/mol as reported in Table 7.

However, four ligands (X, IX, XIV, and VII) have higher binding score (-36.2037, -33.2888, -28.5605, and -27.3758) kcal/mol respectively, ligand (X) formed three interactions metal complex with Mg ion with Glu304, and Arene-Arene interaction with Phe446. Ligand (IX) also formed three interactions metal complex with Mg ion with Asp275, hydrogen bond with Glu304, and Arene-Arene interaction with Phe446. Ligand (XIV) formed two interaction metal complexes with Mg ion with Asp275 and Arene-Arene interaction with Tyr449. Meanwhile ligand (VII) formed five interactions four metal complex with Zn ion with Asp275, Asp392, His238, and His274, the fifth one is hydrogen bond with His234. Figure 4, 5, 6, 7, 8, 9, 10, 11.
**Figure 8**: 3D model of the interaction between compound X and 3o0j binding site.

**Figure 9**: 3D model of the interaction between compound IX and 3o0j binding site.

**Figure 10**: 3D model of the interaction between compound XIV and 3o0j binding site.

**Figure 11**: 3D model of the interaction between compound VII and 3o0j binding site.
4. CONCLUSION

The developed Q SAR model presents a satisfactory correlation with the inhibition activity against PDE4B, and met the criteria for minimum recommended value of validation parameters for a generally acceptable Q SAR model, and molecular docking analysis has shown that all new designed compounds have good interaction to inhibit PDE4B protein. The Q SAR model generated provides a valuable approach for ligand base design, while the molecular docking studies provide a valuable approach for structure base design. These two approaches will be a great help for pharmaceutical and medicinal chemists to design and synthesize new PDE4B inhibitors.

Conflict of interest

The authors declare that they have no conflict of interest.

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