Available online on 15.02.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-21, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use(CC By-NC), provided the original work is properly cited

Open Access Full Text Article

Research Article

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

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

[1, 3] *Department of Chemistry, College of Science, Sudan University of Science and Technology, 2288, Khartoum, Sudan*

[2] *College ofAnimal Production Science and Technology, Sudan University of Science and Technology, 2288, Khartoum, Sudan*

[3] *Department of Chemistry, Ibn Sina University, 10995, Khartoum, Sudan*

Article Info:

Article History:

Received 09 Dec 2020;
Review Completed 23 Jan 2021
Accepted 04 Feb 2021;
Available online 15 Feb 2021

Cite this article as:

Mahgoub Mohamed HH, Mohammed Hussien ABWE, Mohammed Saeed AE, QSAR and docking studies of 3, 5-dimethylpyrazole as potent inhibitors of Phosphodiesterase-4, Journal of Drug Delivery and Therapeutics. 2021; 11(1-s):86-93
DOI: http://dx.doi.org/10.22270/jddt.v11i1-s.4718

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 (r^2) of 0.872, and leave-one-out (LOO) cross-validation coefficient (Q^2) value of 0.733. The predictive power of the developed model was confirmed by the external validation which has (r^2) 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 (IC_{50} = 0.2813, 0.5814, 0.6929, 0.6125µM, respectively) against PDE4B compared to the reference rolipram with (IC_{50}=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 -33.2888 kcal/mol respectively.

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

*Address for Correspondence:

Hiba Hashim Mahgoub Mohamed

Department of Chemistry, College of Science, Sudan University of Science and Technology, 2288, Khartoum, Sudan
Department of Chemistry, Ibn Sina University, 10995, Khartoum, Sudan

1. INTRODUCTION

Phospho**die**sterase (PDE) are ubiquitous super family of enzymes that hydrolyze the phosphodiester bond and subsequent inactivation of second messenger molecules **c**yclic **a**denosine **mono**phosphate (cAMP) and **c**yclic **g**uanosine **mono**phosphate (cGMP)[1], they involved in the regulation of almost all physiological processes. In airway smooth muscle, inflammatory cell, and immune cells[2, 3]. The PDE enzymes consist of 11 families (PDE1 - PDE11) based on sequence homogeneity, inhibitor sensitivity, and biochemical properties[4-6], they can be classified into three categories based on their substrate specificity. PDE4, PDE7, and PDE8 selectively hydrolyze cAMP[7], 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 isoform[8]. 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 differentiation[9].

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 function[10, 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-monophosphate[12, 13]. PDE4 isoforms expression is ubiquitous. PDE4A is highly expressed in brain, cardiovascular tissues, and small intestine cell[14, 15], PDE4B and PDE4D highly expressed in immune cells[16, 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 **c**hronic **o**bstructive **p**ulmonary **d**isorder (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 **s**tructure – **a**ctivity **r**elationship (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 determine toxicity or any desired biological effects of candidate compounds for new therapeutic molecules[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[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 (I-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

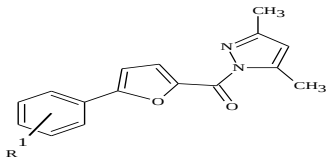
A set of 13 derivatives of 3, 5-dimethylpyrazole containing furan moiety as PDE-4 inhibitors reported by Hu *et al* (2018) [22] was used in the present study, their inhibition activity against PDE4Bwere expressed as (IC_{50}) values half maximal inhibitory concentration. The (IC_{50}) values were converted into the corresponding (pIC_{50}) using the formula: $pIC_{50} = -\log IC_{50}$, values and structures of the 3, 5-dimethylpyrazole derivatives are listed in Table1.

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 comprises 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 Table2.

Table 1: Biological activities and structures of 3, 5-dimethylpyrazole derivatives [22]



Compound	R^1	IC_{50}	pIC_{50}
1	4-Cl	3.90	5.409
2	4-F	7.20	5.143
3	4-NO_2	15.40	4.812
4	4-CH_3	8.40	5.076
5	4-OCH_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_2	35.90	4.445
10	2-Cl	52.40	4.281
11	2-NO_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	1.0663	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 (pIC_{50}) 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.

$$pIC_{50} = 21.82904 - 1.10399 \times \log P(o/w) + 1.49422 \times HOMO \quad (1)$$

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

r	r^2	Q^2	s	F	RMSE	*P* value
0.934	0.872	0.733	0.185	54.640	0.165	0.000

Table 4: Experimental and predicted pIC_{50} for training set and cross validation against PDE4B.

Compd	$pIC_{50exp.}$	$pIC_{50pred.}$	Residuals	$CV_{pred.}$	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 pIC_{50}values of test set

Compd	$pIC_{50exp.}$	$pIC_{50pred.}$	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

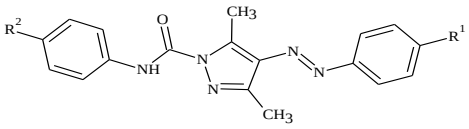
To evaluate robustness of the model, internal validation was performed to the training set using leave-one-out (LOO) cross-validation method. The cross-validated regression coefficient (Q^2) values were thereafter calculated according to the equation (1). External validation was performed in order to 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.

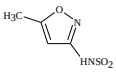
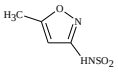
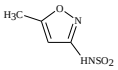
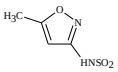
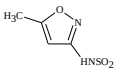
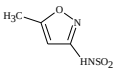
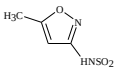
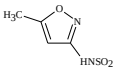
2.1.5. Predict the activity of designed 3, 5-dimethyl-pyrazole derivatives (I-XV)

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 pIC_{50} along with the structures listed in Table 6.

Table 6: Structures and predicted pIC_{50} values for designed 3, 5-dimethylpyrazole derivatives against PDE4B.



I - XV

Compd	R^1	R^2	$pIC_{50pred.}$
I	H_2NO_2S-	-	5.4560
II	H_2NO_2S-	Br	4.5091
III	H_2NO_2S-	H_2NO_2S-	6.5508
IV	H_2NO_2S-		5.1826
V	H_2NO_2S-		6.2355
VI		-	3.9519
VII		Br	3.0463
VIII		H_2NO_2S-	5.1352
IX			3.6015
X			4.7950
XI		-	4.9759
XII		Br	4.0290
XIII		H_2NO_2S-	6.1593
XIV			5.0846
XV			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 build 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 Table7.

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 (A°)
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	-
		Tyr449	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 pIC_{50} values for training set, cross-validation and test set compounds against PDE4B respectively.

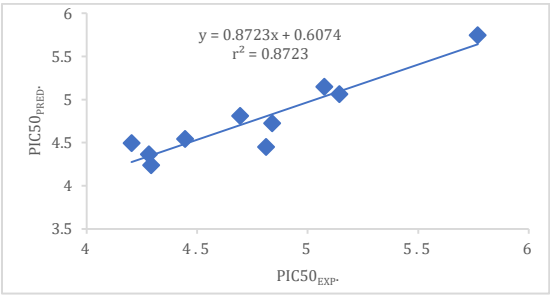


Figure 1: Predicted versus experimental pIC_{50}values of training set against PDE4B.

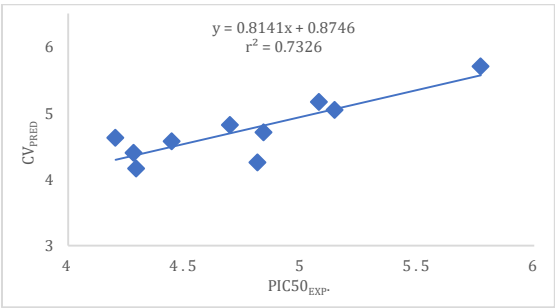


Figure 2: Predicted versus experimental pIC_{50}values of cross validation against PDE4B.

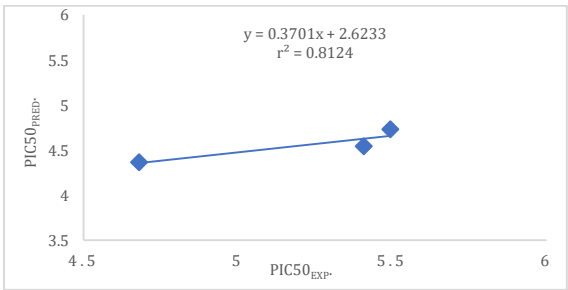


Figure 3: Predicted versus experimental pIC_{50} values of test set against PDE4B.

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 -8.9797kcal/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 Asp275, hydrogen bond 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.

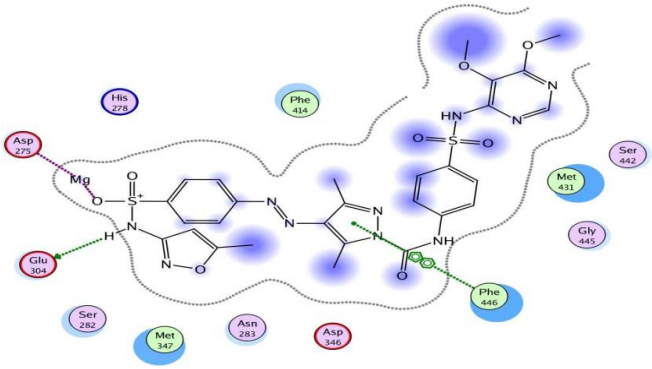


Figure 4: 2D molecular docking model of compound X with 3o0j.

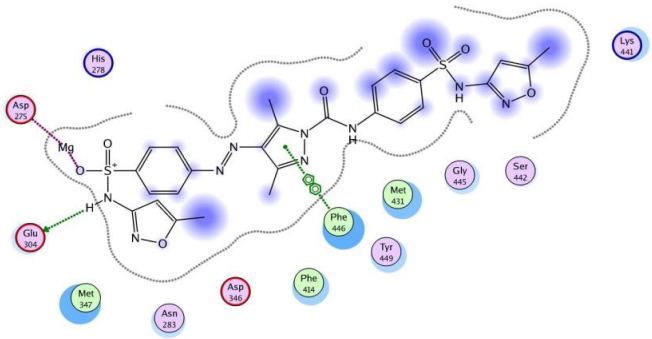


Figure 5: 2D molecular docking model of compound IX with 3o0j.

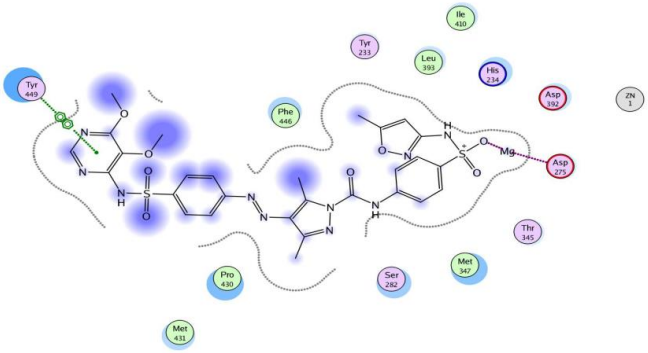


Figure 6: 2D molecular docking model of compound XIV with 3o0j.

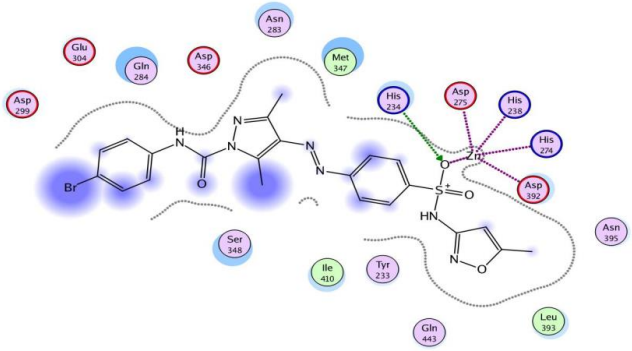


Figure 7: 2D molecular docking model of compound VII with 3o0j.

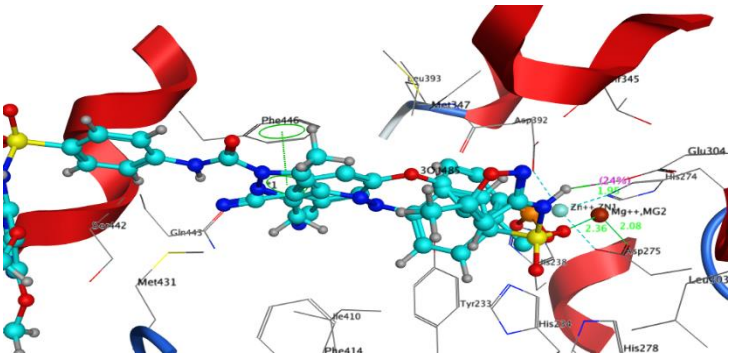


Figure 8: 3D model of the interaction between compound X and 3o0j binding site.

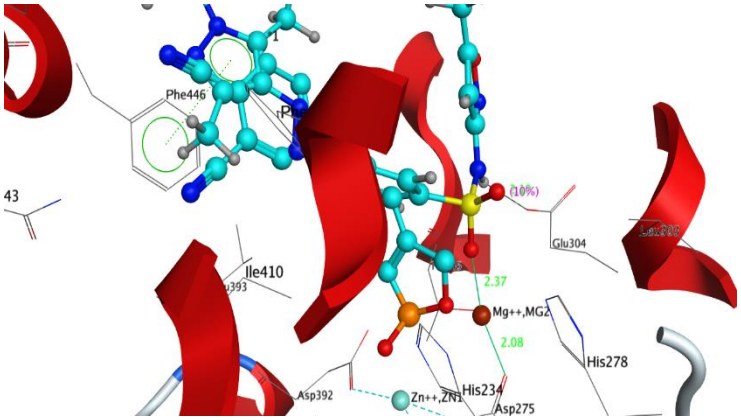


Figure 9: 3D model of the interaction between compound IX and 3o0j binding site.

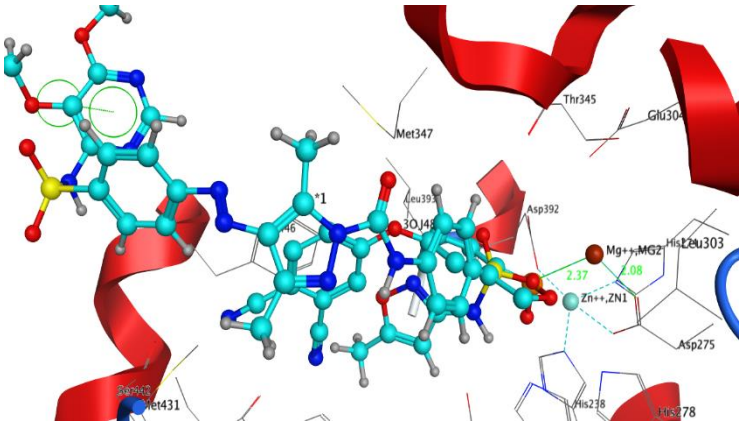


Figure 10: 3D model of the interaction between compound XIV and 3o0j binding site.

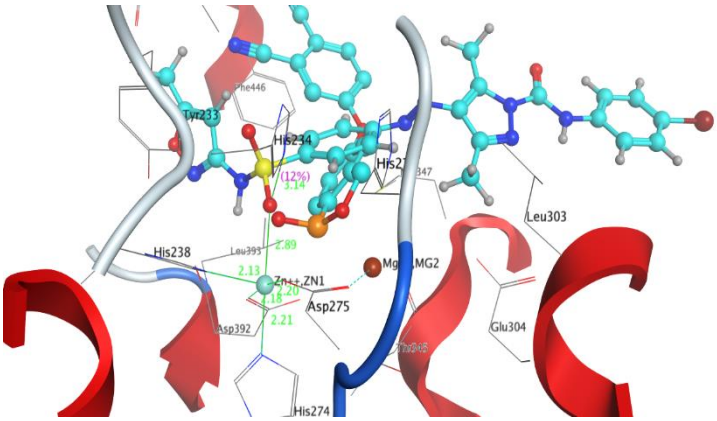


Figure 11: 3D model of the interaction between compound VII and 3o0j binding site.

4. CONCLUSION

The developed QSAR 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 QSAR model, and molecular docking analysis has shown that all new designed compounds have good interaction to inhibit PDE4B protein. The QSAR 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 interest

The authors declare that they have no conflict of interest.

REFERENCES

[1]. Li H, Zuo J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. Front. Pharmacol. 2018; 9:1048.

[2]. Chiricozzi A, Caposiena D, Garofalo V, Cannizzaro MV, Chimenti S, Saraceno R. A new therapeutic for the treatment of moderate to severe plaque psoriasis: apremilast. Expert review of clinical immunology. 2016; 12(3):237-249.

[3]. Ahmed F, Murata T, Shimizu K, Degerman E, Maurice D, Manganiello V. Cyclic nucleotide phosphodiesterses: important signaling modulators and therapeutic targets. Oral diseases. 2015; 21(1):e25-e50.

[4]. Halpin DM. ABCD of the phosphodiesterase family: interaction and differential activity in COPD. International journal of chronic obstructive pulmonary disease. 2008; 3(4):543.

[5]. Keravis T, Lugnier C. Cyclic nucleotide phosphodiesterase (PDE) isozymes as targets of the intracellular signaling network: benefits of PDE inhibitors in various diseases and perspectives for future therapeutic developments. British journal of pharmacology. 2012; 165(5):1288-1305.

[6]. Maurice DH, Ke H, Ahmed F, Wang Y, Chung J, Manganiello VC. Advances in targeting cyclic nucleotide phosphodiesterases. Nature reviews drug discovery. 2014; 13(4):290-314.

[7]. Vang AG, Basole C, Dong H, Nguyen RK, Housley W, Guernsey L, Adami AJ, Thrall RS, Clark RB, Epstein PM, Brocke S. Differential expression and function of PDE8 and PDE4 in effector T cells: implications for PDE8 as a drug target in inflammation. Frontier in pharmacology. 2016; 7:259.

[8]. Conti M, Beavo J. Biochemistry and physiology of cyclic nucleotide phosphodiesterases: essential components in cyclic nucleotide signaling. Annu. Rev. Biochem. 2007; 76:481-511.

[9]. Omori K, Kotera J. Overview of PDEs and their regulation. Circulation research. 2007; 100(3):309-327.

[10]. Houslay MD. PDE4 cAMP-specific phosphodiesterases. Prog. Nucleic Acid Res. Mol. Biol. 2001; 69:249-315.

[11]. Houslay MD, Schafer P, Zhang KY. Keynote review: phosphodiesterase-4 as a therapeutic target. Drug discovery today.2005; 10(22):1503-1519.

[12]. Michalski JM, Golden G, Ikari J, Rennard SI. PDE4: a novel target in the treatment of chronic obstructive pulmonary disease. Clinical Pharmacology and Therapeutics. 2012; 91(1):134-142.

[13]. Martinez A, Gil C. cAMP-specific phosphodiesterase inhibitors: promising drugs for inflammatory and neurological diseases. Expert opinion on therapeutic patents. 2014; 24(12):1311-1321.

[14]. Yu H, Zhong J, Niu B, Zhong Q, Xiao J, Xie J, Lin M, Zhou Z, Xu J, Wang H. Inhibition of phosphodiesterase 4 by FCPR03 alleviates chronic unpredictable mild stress-induced depressive-like behaviors and prevents dendritic spine loss in mice hippocampi. International Journal of Neuropsychopharmacology. 2019; 22(2):142-155.

[15]. Richter W, Xie M, Scheitrum C, Krall J, Movsesian MA, Conti M. Conserved expression and functions of PDE4 in rodent and human heart. Basic research in cardiology. 2011; 106:249-262.

[16]. Wittmann M, Helliwell PS. Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. Dermatology and theraby. 2013; 3(1):1-15.

[17]. Singh D, Beeh KM, Colgan B, Kornmann O, Leaker B, Watz H, Lucci G, Geraci S, Emirova A, Govoni M, Nandeuil MA. Effect of the inhaled PDE4 inhibitor CHF6001 on biomarkers of inflammation in COPD. Respiratory research. 2019; 20(1):180.

[18]. Brown WM. Treating COPD with PDE4 inhibitors. International journal of chronic obstructive pulmonary disease. 2007; 2(4):517-533.

[19].Halder AK, Moura AS, Cordeiro MND. QSAR modeling: a therapeutic patent review 2010-present. Expert opinion on therapeutic patents. 2018; 28(6):467-476.

[20]. Tropsha A. Best practices for QSAR model development, validation, and exploitation. Molecular informatics. 2010; 29(6-7):476-488.

[21]. Lima AN, Philot EA, Trossini GHG, Scott LPB, Maltarollo VG, Honorio KM. Use of machine learning approaches for novel drug discovery. Expert opinion on drug discovery. 2016; 11(3):225-239.

[22]. Hu DK, Zhao DS, He M, Jin HW, Tang YM, Zhang LH, Song GP, Cui ZN. Synthesis and bioactivity of 3, 5-dimethylpyrazole derivatives as potential PDE4 inhibitors. Bioorganic and medicinal chemistry letters. 2018; 28(19):3276-3280.