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COMPUTER AIDED DRUG DESIGN OF PDE 4 INHIBITORS FOR POTENTIAL THERAPY AGAINST CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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ABSTRACT
Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory disease. it is collection of lung diseases including chronic bronchitis, emphysema and chronic obstructive airways disease. COPD is characterized by persistent airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases. In the inflammatory cells cAMP plays the role of a negative regulator of the primary activating pathways such as cytokine release by T-cells. Levels of cAMP on the other hand are regulated by cAMP-specific PDE isozymes (e.g., PDE4 predominantly expressed in inflammatory and immune cells in addition to brain). Inhibition of the PDE4 in these cells effectively elevates the intracellular cAMP levels, thereby activating specific protein phosphorylation cascades that elicit a variety of functional responses. Additionally, elevation of intracellular cAMP levels via inhibition of PDE4 activity led to smooth muscle relaxation and thereby bronchodilation that is beneficial for the management of respiratory diseases like COPD.

KEY WORDS- *Chronic Obstructive Pulmonary Disease (COPD), Chronic Bronchitis, Emphysema, T-cells, protein phosphorylation, bronchodilation.*

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease. it is collection of lung diseases including chronic bronchitis, emphysema and chronic obstructive airways disease. COPD is characterized by persistent airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases. It is a major public health burden, with a global prevalence of 10.1%, causing 3 million deaths worldwide in 2011 and predicted to be the fourth leading cause of death by 2030.

Mechanism of inflammation in COPD: The processes underlying COPD are not yet fully understood, however chronic inflammation appears to have an important role.

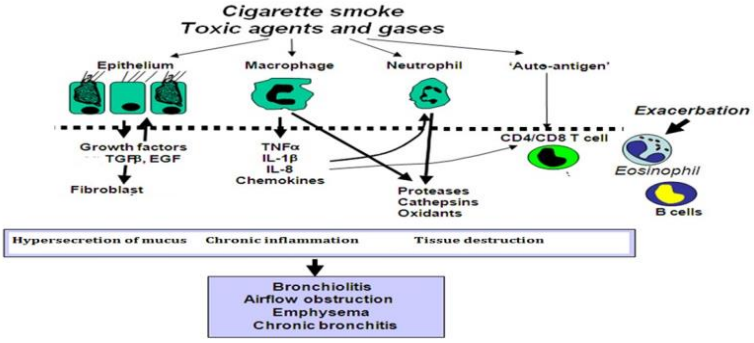

Figure 1: Mechanism of action of COPD

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Inflammation plus structural alterations occurring in the small airways and lung parenchyma, such as fibrosis, smooth muscle hypertrophy, goblet cell metaplasia and lumen occlusion by mucus plugging, are major contributors to the airflow limitation and accelerated decline of forced expiratory volume in one second (FEV1) observed in COPD.

Risk factors for COPD: The main cause of COPD is smoking. The likelihood of developing COPD increases with smoking. Over many years, the inflammation leads to permanent changes in the lung. The walls of the airways thicken and more mucus is produced. Damage to the delicate walls of the air sacs in the lungs causes emphysema and the lungs lose their normal elasticity. The smaller airways also become scarred and narrowed. These changes cause the symptoms of breathlessness, cough and phlegm associated with COPD.

Phosphodiesterase 4 (PDE4)

Phosphodiesterase 4 (PDE4) is the predominant cAMP-degrading enzyme expressed in inflammatory cells. PDE4 family is comprised of 4 genes (PDE4A to D)with a unique chromosomal location per gene.[34] Due to alternative splicing of the genes, multiple splice varients are reported and classified into two main groups, the long and short forms. All subtypes provide a conserved catalytic domain of (~ 270 amino acids) and the absence or presence, respectively of the short and long form, two additional regions UCR1 (Upstream conserved region) and UCR2 within the N-terminus.PDE4A, PDE4B and PDE4D gene products are found in most immune and inflammatory cells.

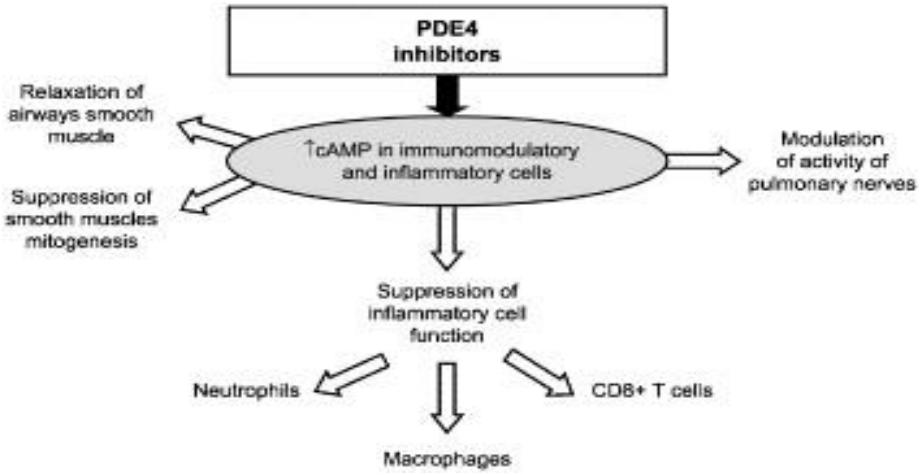

Figure 2: Mechanism of action of PDE 4

2. RESEARCH ENVISAGED AND PLAN OF WORK

COPD is characterized by persistent airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles, gases and tobacco smoke. It is a major public health burden, with a global prevalence of 10.1%, causing 3 million deaths worldwide in 2011 and predicted to be the fourth leading cause of death by 2030.The drugs used in the treatment of COPD have not appreciably changed in the last 25 years and as a result there is clearly a need for novel therapeutic agents to reduce disease progression and possibly reverse the decline in lung function seen with disease.
Phosphodiesterase 4 (PDE4) is a cAMP specific phosphodiesterase expressed in inflammatory cells such as eosinophils. Inhibition of PDE4 results in elevation of cAMP in these cells, which in turn down regulates the inflammatory response.

3. EXPERIMENTAL (SAR)

The Computer aided drug design (CADD) studies were performed in Window based system Intel Core Pentium processor. QSAR studies were performed on V-Life MDS (Molecular Design Suite) provided by V-Life Sciences Technologies Pvt. Ltd., Pune, India.

QSAR analysis (Quantitative Structure Activity relationship)

Quantitative structure-activity relationships (QSAR) studies are used for prediction of biological activities of the compound. itis an attempt to correlate 2D and 3D properties (descriptors) of compounds with biological activities. The QSAR relationship can be expressed as a mathematical equations and graphical plots.

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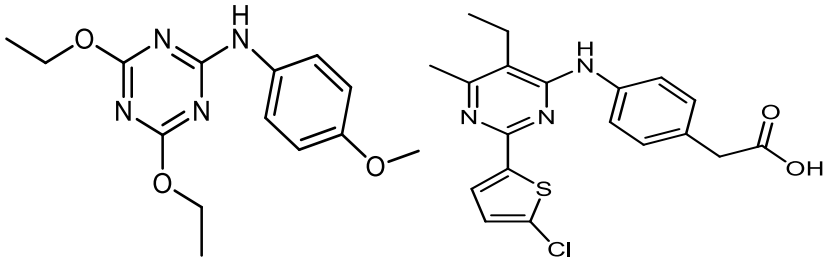
2D-QSAR

1. Molecule sketching (Chemdraw ultra 12.0)
2. Energy minimization (Molecular Merck force field)
3. Calculation of 2d descriptors
4. Data selection
5. Selection of training and test set (Using random data selection)
6. Statistical analysis (using pls regression)

Molecular sketching:

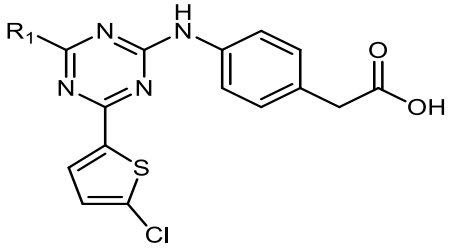
All structure of the compounds were sketched by using Chemdraw Ultra 12.0 software.2D structures were converted into 3D by importing to V-Life MDS andsaved as .mol2 file.



1 2

Figure 3: Structure of lead compound 1 and 2

Table. 1: Structure of Inhibitory activity of R1 triazine analogs



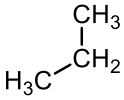
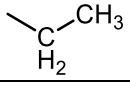
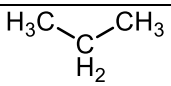
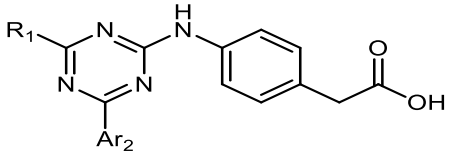
S. No.	R	IC50	-log IC50
3.		**1287**	**-3.10958**
4.		**1945**	**-3.28892**
5		**383**	**-2.5832**
6		**2447**	**-3.38863**

Table 2: Structure of Inhibitory activity of Ar_2 analogs



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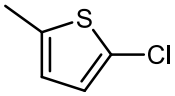
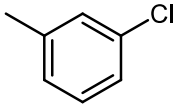
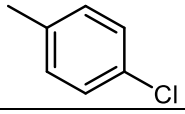
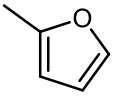
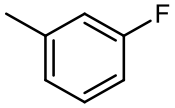
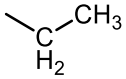
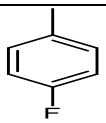
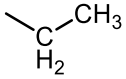
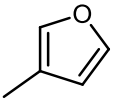
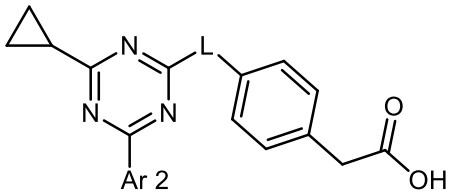
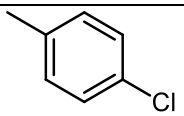
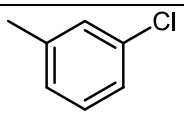
S.NO	R_1	Ar_2	IC50	-log IC50
7			251	-2.39967
8			237	-2.37475
9			3770	-3.57634
10	$-CH_3$		18755	-4.27312
11			1437	-3.15746
12			1460	-3.16435
13			2777	-3.44358

Table 3: Structure of Inhibitory activity of linker modified analogs



S. No	L	Ar_2	IC50	-log IC50
14	$NHCH_2$		2282	-3.35832
15	$NHCH_2$		845	-2.92686

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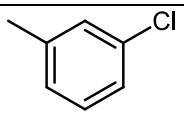
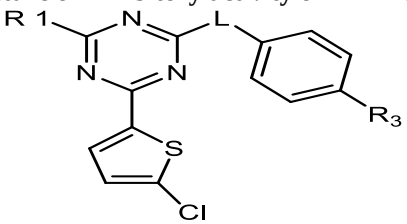
16	O		1862	-3.26998

Table 4: Structure of Inhibitory activity of Ar1 modified analogs



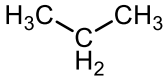
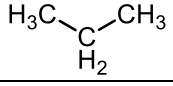
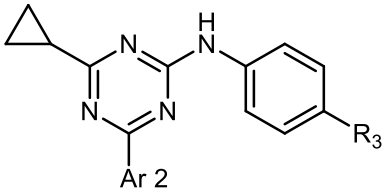
S. No.	R_1	R_3	IC_{50}	-log IC_{50}
17	$-CH_3$	$-CO_2H$	4048	-3.60724
18	$-CH_2\ CH_3$	$-CO_2H$	261	-2.41664
19	$-CH_2\ CH_3$	-F	1394	-3.14426
20		$-CO_2H$	220	-2.34242
21		-F	8815	-3.94522

Table 5:Structure of Inhibitory activity of Ar1 substitution



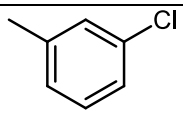
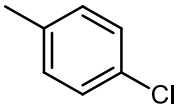
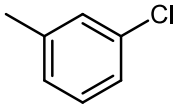
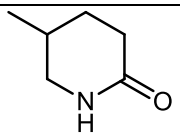
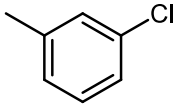
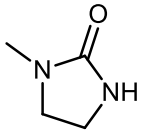
S. No.	Ar_2	R_3	IC_{50}	-log IC_{50}
22		$-CO_2H$	46	-1.66276
23		$-CO_2H$	135	-2.13033
24			135	-2.13033
25			Inactive	#VALUE!

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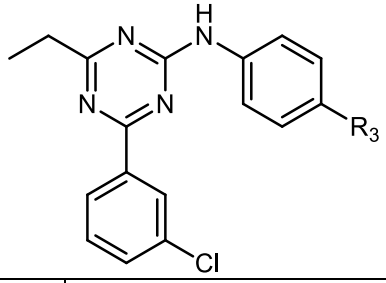
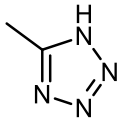
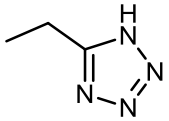
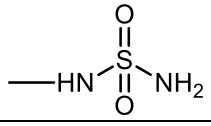
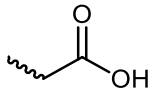
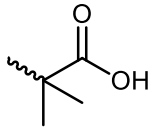
Table 6: Inhibitory activity of Ar1 substitution



S. No	R_3	IC_{50}	-log IC_{50}
26	CH_2CO_2H	781	-2.89265
27	$-CO_2H$	281	-2.38202
28	CN	12	-1.07918
29	CH_2CN	165	-2.21748
30		126	-2.10037
31		69	-1.83885
32		402	-2.60423
33		1090	-3.03743
34		1574	-3.197

4. RESULTS AND DISCUSSION

Results of 2D-QSAR analysis

QSAR models were generated by using partial least square (PLS) regression method coupled with stepwise forward-backward method. Various models were generated and the best model was chosen based on the value of the statistical parameters. Summary of the best model is given below:

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Table 7: Best Models of 2D QSAR

S. No	Model I	Model II	Model III
N	23	23	23
Df	20	20	20
r2	0.7876	0.7637	0.7231
q2	0.7146	0.6153	0.6307
F_test	37.0776	32.3165	26.1088
r2_se	0.3470	0.4604	0.3883
q2_se	0.4023	0.5875	0.4484
pred_r2	0.6225	0.6165	0.6367
pred_r2se	0.3374	0.4341	0.4364

Test Set	1 , 3 , 9, 12, 16, 17, 19, 24 , 32, 34	
Statistical	**n**=23	**degree of freedom**= 20
Parameters	**r^2**=0.7876	**q^2**= 0.7146
	F-test= 37.0776	**r^2 se**= 0.347
	q^2 se= 0.4023	**pred_r^2**=0.622
	pred_r^2se= 0.3374	
Equation	**pIC50 =0.2373 Saa CHE - index -0.3692 Sss CH2 Count + 0.0083 SA Hydrophobic Area**	

The equation explains 78 % (r^2 = 0.7876) of the total variance in the training set. It also has an internal (q^2) and external (pred_r^2) predictive ability of ~71 % and ~62% respectively. Low standard error of r^2_se= 0.33, q^2_se=0.40 and pred_r^2se = 0.34 demonstrates accuracy of the model. The F-test = 37.5323 shows the statistical significance of 99.99% of the model which means that probability of failure of the model is 1 in 10000. In addition, the randomization test shows confidence of ~ 99.9 % that the generated model is not random and hence it is chosen as the QSAR model.

The plot of observed vs. predicted activity (Fig.**)** provides an idea about how well the model was trained and how well it predicts the activity of the external test set. From the plot it can be seen, model is able to predict the activity of training set quite well (all red points are close to regression line) as well as external test set up to ~60% (only 1 blue point is relatively apart from the regression line) providing confidence in predictive ability of the model.

5. SUMMARY AND CONCLUSION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease. it is collection of lung diseases including chronic bronchitis, emphysema and chronic obstructive airways disease.. It is the fourth leading cause of death worldwide. PDE4 has 20 isoenzymes encoded by 4 genes (PDE4A, PDE4B, PDE4C and PDE4D). Through research it has been found that inhibition of PDE4D is responsible for the dose related side effects. Selective inhibitors of PDE4B can alleviate the disease as well as combat the dose related side effects.

2D-QSAR

QSAR analysis was performed by using V-life MDS software 4.4. Partial least square regression analysis was used to derive 2D QSAR model.The best model was selected on the basis of high correlation coefficient, less standard error of estimation, high internal predictivity and high F- value.

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CONCLUSION

In the model, three descriptors viz. Saa CHE, SsssCH2 count and SA Hydrophobic area were found to show good correlation with the biological activity. Out of the three, Saa CHE and SA Hydrophobic Area are directly proportional to the activity while SsssCH2 count is inversely proportional to the activity. Saa CHE-index: Electrotopological state indices for number of –CH group connected with two aromatic bonds. SssCH2 count, This descriptor defines the total number of –CH2 group connected with two single bonds will have poor biological activity. SA Hydrophobic Area, vdW surface descriptor showing hydrophobic surface area. This observation is supported by molecules of the Triazines series on which the study was performed.

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