





30		8.090	7.618	7.846
31		8.110	7.610	7.559
32		8.240	7.618	8.005
33		8.310	7.619	8.015
34		8.380	8.540	8.323
35		8.880	7.928	9.208
36		9.0300	9.008	8.425
37		9.330	8.443	9.646

#### Test set molecules

1		5.670	5.991	6.037
2		6.380	5.816	6.446
3		6.660	6.133	6.417
4		6.770	5.979	6.495
5		6.950	7.608	6.919
6		6.960	7.611	6.857
7		7.040	7.730	6.331
8		7.406	6.444	6.891

9		7.420	7.832	7.481
10		7.680	7.618	7.139
11		8.000	9.026	9.407
12		8.190	8.726	8.114
13		8.850	9.012	8.164
14		9.40	9.055	9.057
15		9.720	9.374	9.547

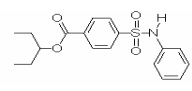
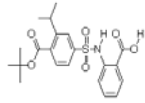
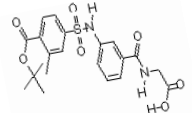
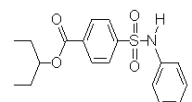
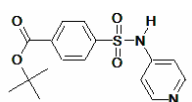
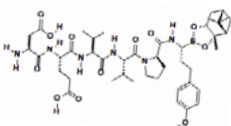
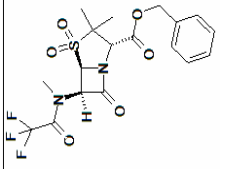
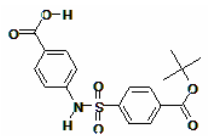
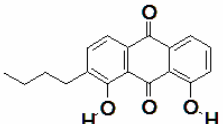
Catalyst version 4.7 was used to generate Pharmacophore models. 21 molecules forming the training set were used to generate Hypogen hypothesis.

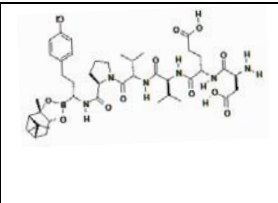
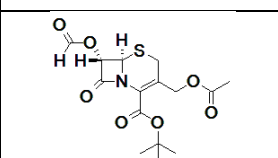
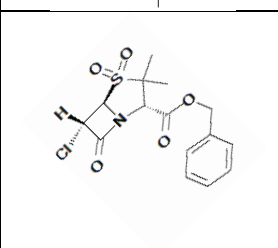
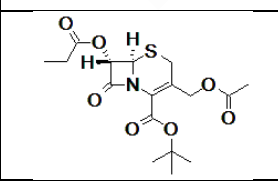
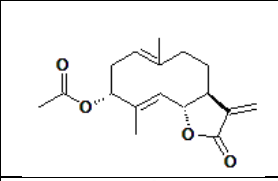
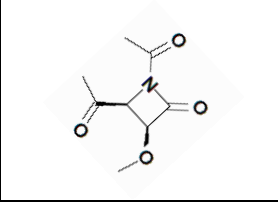
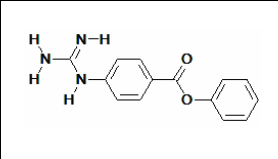
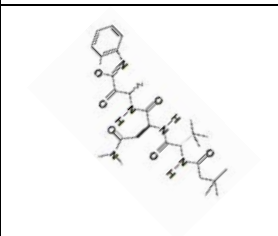
**Table 2:** Statistical Parameters for MFA and RSA

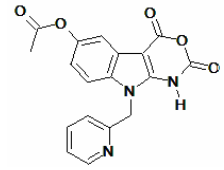
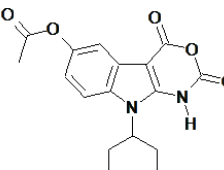
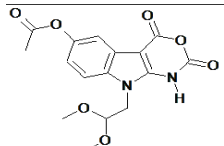
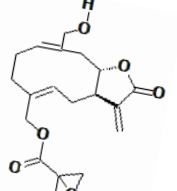
Statistical Parameters	MFA RSA	
R <sup>2</sup>	.839	.856
XVR <sup>2</sup>	.793	.739
Outliers	2	2
BSR <sup>2</sup>	.845	.798
BSR <sup>2</sup> ERROR	.002	.013
PRESS	10.56	9.26

All structures were built and minimized within the Catalyst software package, and conformational analysis of each molecule was implemented using the poling algorithm. Hypotheses were generated from a collection of conformational models of compounds spanning activities of 4-5 orders of magnitude.

**Table 3.1:** Training Set with Experimental and Predicted Activity

M.. No	Structure	IC50		Error F	it Value	Activity Scale	
		Experimental Pr	redicted			Exp	Pre
1		0.001	0.013	1.3	9.42	+++	+++
2		0.092	0.22	2.4	7.59	+++	+++
3		0.12	0.14	1.2	7.87	+++	+++
4		0.27	0.22	1.2	7.48	+++	+++
5		0.4	2.9	7.3	6.66	+++	++
6		0.56	0.366	1.5	7.4	+++	+++
7		0.7	2.3	3.2	7.35	+++	++
8		0.97	2.5	2.6	6.80	+++	++
9		1.4	1.2	1.2	6.89	++	++

10		6.4	2.2	2.9	6.25	++	++
11		10	15	1.5	5.95	++	++
12		14	6.4	2.2	5.47	++	++
13		36	23	1.5	5.79	++	++
14		70	73	1	5.70	++	++
15		94	1100	12	4.10	++	+
16		150	310	2.1	4.21	+	+
17		180	13	14	6.25	+	++

18		290	350	1.2	4.21	+	+
19		450	300	1.5	4.45	+	+
20		740	320	2.3	4.21	+	+
21		1000	100	9.9	5.73	+	+

## Results and discussion:

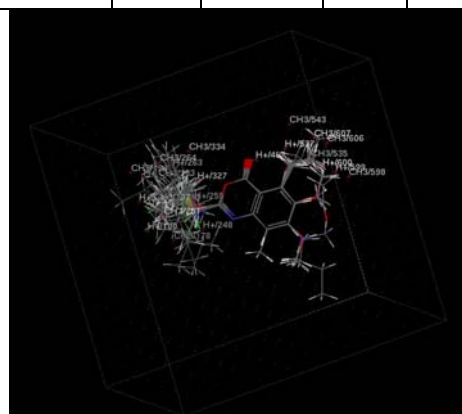
### *Molecular field analysis (MFA)*

The regression analysis on training set molecules produced a QSAR model and is shown in eq. 1

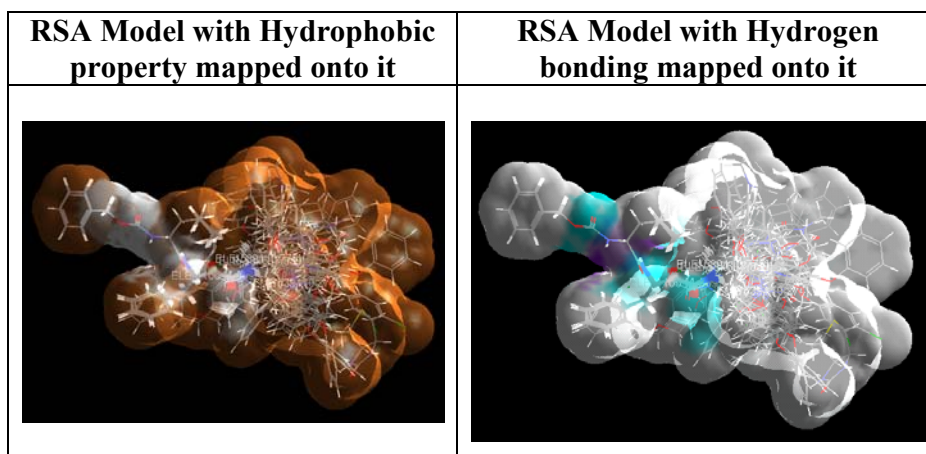
$$\text{Activity} = -0.046748 * \text{"CH3/334"} + 0.03696 * \text{"H+/467"} + 0.04704 * \text{"CH3/543"} - 0.027816 * \text{"H+/600"} + 0.042922 * \text{"CH3/193"} + 0.064957 * \text{"CH3/187"} - 0.025432 * \text{"CH3/606"}$$

### *Receptor surface analysis (RSA)*

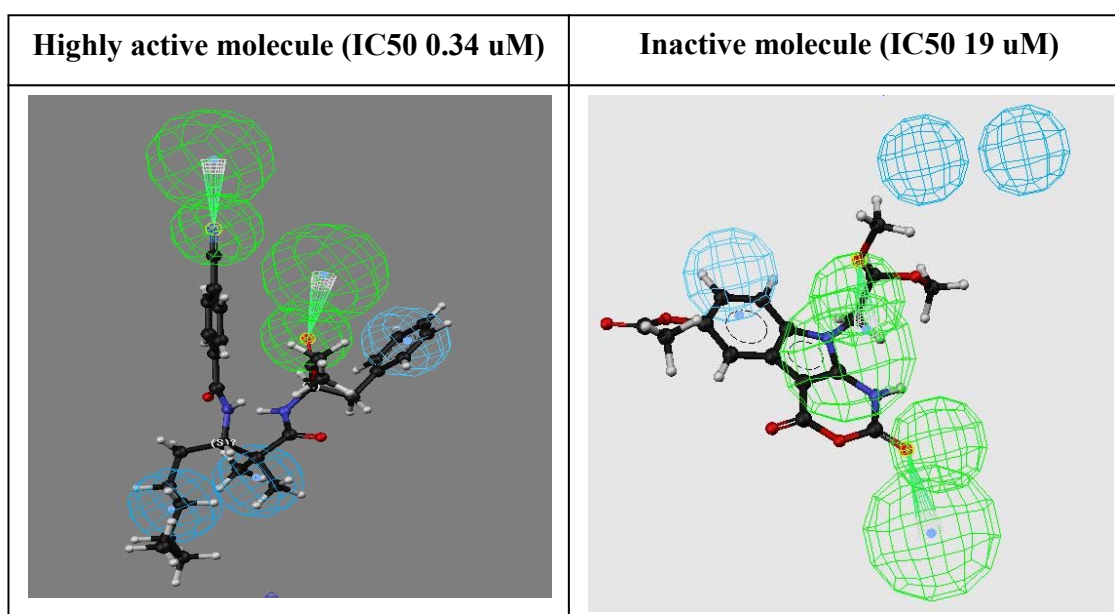
The QSAR model generated by RSA is represented as eq 2



**Fig 1:** Molecular Field Analysis Grid (3D-QSAR studies)



**Fig 2: Receptor Surface Models**



**Fig 3: Pharmacophore Mapping**

$$\begin{aligned} \text{Activity} = & -0.90135 - 34.8009 * \\ & \text{"ELE/1380"} + 36.9685 * \text{"VDW/1104"} \\ & - 1.6223 * \text{"ELE/2615"} - 1.73236 * \\ & \text{"VDW/1618"} - 4.48241 * \text{"ELE/1974"} \\ & + 9.67656 * \text{"VDW/2150"} - 4.50458 * \\ & \text{"ELE/2344"} \end{aligned}$$

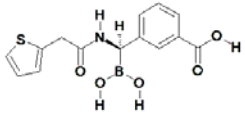
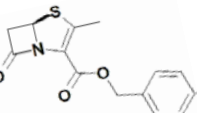
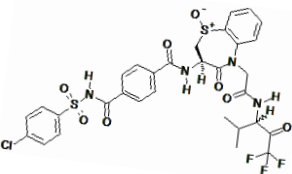
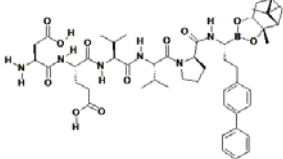
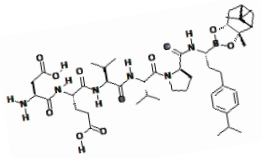
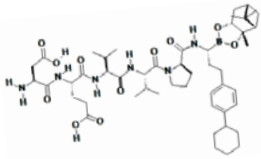
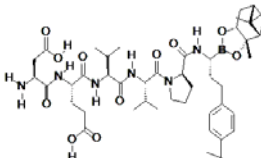
The statistical parameters for MFA and RSA are given in Table 2. The Stereo view of rectangular molecular field surrounding aligned molecules and receptor surface which represents the virtual active site is shown in Fig 1 and 2 respectively.

### Pharmacophore Hypothesis Generation:

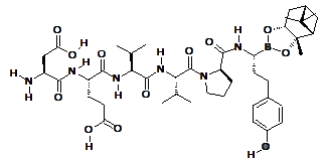
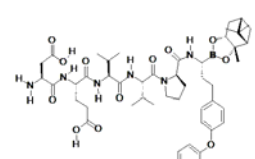
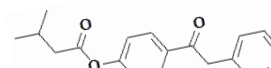
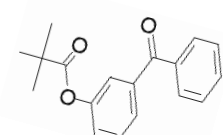
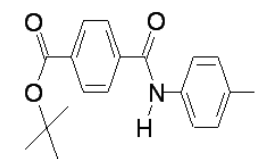
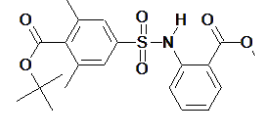
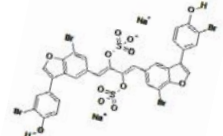
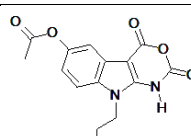
Training set consists of 21 compounds tested against HLE was used to develop Pharmacophore hypotheses. A total of 10 hypotheses were generated and its different cost values, correlation coefficients (r), RMS deviations, and pharmacophore feature definitions are listed in Table 3.

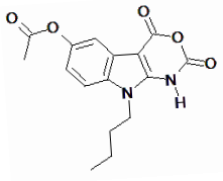
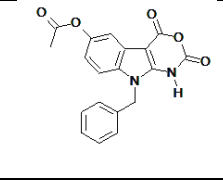
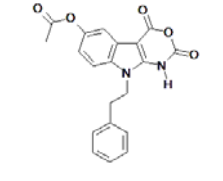
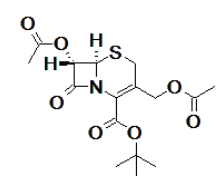
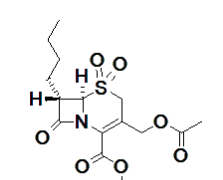
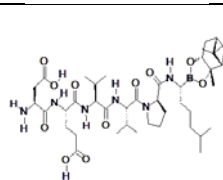
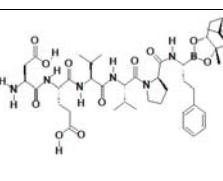
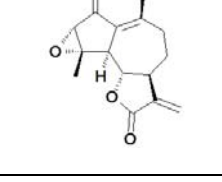
For the training set the accuracy in predicting active and inactive compounds was 80%.

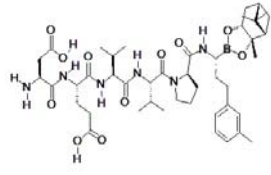
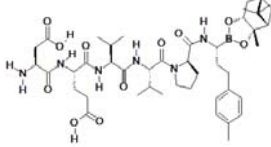
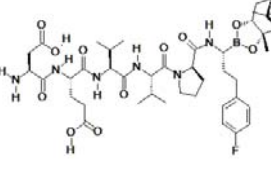
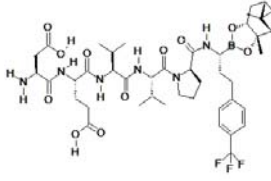
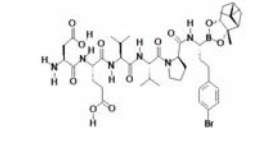
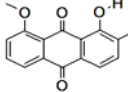
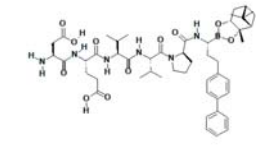
**Table 3.2: Test Set with Experimental and Predicted Activity**

M.No S	structure	IC50 $\mu$ M		Error	Activity Scale	
		Exp P	redicted		Exp	Predicted
22		500	350	-1.4	+	+
23		15	28	1.9	++	++
24		6.8	14	21	+++	++
25		0.9	4.6	5.2	+++	+++
26		0.45	4.1	9.2	+++	+++
27		0.4	4.6	1.2	+++	+++
28		0.34	4.2	12	+++	+++



29		0.9	5	5.6	+++	+++
30		0.22	4.4	20	+++	+++
31		1.9	18	9.6	+++	++
32		6.66	29	4.4	+++	++
33		100	13	-7.6	++	++
34		0.96	6.8	7	+++	+++
35		0.47	7.3	16	+++	+++
36		17.5	12	-1.5	++	++

37		665	410	-1.6	+	+
38		810	400	-1.6	+	+
39		75	510	6.8	+	+
40		92	650	7.1	++	+
41		40	24	-1.7	++	++
42		40	64	-1.6	++	++
43		7.3	23	3.1	+++	++
44		3.5	6.6	1.9	+++	+++

45		110	49	-1.2	+	++
46		5.7	4.9	-1	+++	+++
47		5	4.8	-1	+++	+++
48		0.8	9.9	12	+++	+++
49		1.8	4.5	2.5	+++	+++
50		1.6	5	3.1	+++	+++
51		19	6.2	-3.1	++	++

+ = Low active    ++ = Moderately active    +++ = Highly active

**Table 3.3:** 10 Pharmacophore Hypotheses Generated Using 21 Training Set Molecules

Hypothesis number	Total Cost	Cost diff (null-Total)	RMS deviation	Training set correlation (r)	Features	Test set Correlation (r)
1	100.857	79.028	1.06899	.9435567	A ,A ,H ,H ,Z	.819387
2	106.066	73.819	1.18453	.931674	A ,A ,H ,Z	.809371
3	107.143	72.742	1.32568	.911664	A ,A ,H ,H ,Z	.757693
4	107.506	72.379	1.34072	.909527	A ,A ,H ,H ,Z	.71806
5	108.263	71.662	1.36745	.905694	A ,A ,H ,H ,Z	.65848
6	108.772	71.113	1.38425	.903245	A ,A ,H ,H ,Z	.62456
7	109.26	70.625	1.33177	.911934	A ,A ,H ,Z	.618473
8	109.551	70.334	1.40963	.899473	A ,A ,H ,H ,Z	.795995
9	110.854	69.031	1.42659	.897321	A ,A ,H ,H	.759223
10	111.13	68.775	1.46328	.891099	A ,A ,H ,H ,Z	.661418

A = hydrogen bond acceptor    H = hydrophobic aliphatic    Z = hydrophobic aromatic

extremely grateful to Dr. J. A. R. P. Sarma, GVK Biosciences for providing

The selected pharmacophore hypothesis yielded a RMS deviation of 1.06 and a correlation coefficient of 0.943 with a cost difference of 79.02. The best pharmacophore model was validated on 50 test molecules to give correlation value of 0.846. For the test set, the accuracy in predicting active compounds was greater than 10 %, while 16% and 8% representing both false positive and negative respectively. The mapping of Hypothesis model onto an active and inactive training set compound is shown in Fig 3.

#### Conclusion:

The 3D QSAR studies show that hydrophobic groups are responsible for increase in activity, which shows that RSA model predicts better than MFA. Further, the knowledge of this four-feature pharmacophore hypothesis for Human Leukocyte Elastase inhibitors can be very useful for virtual screening to design more potent lead moieties for the treatment of various types of COPD.

#### Acknowledgement:

We sincerely thank Sai BioSciences Research Institute (SBRI), Chennai for providing lab facilities and we are

NOC to process part of our research in their lab.

#### References:

- [1] Michael Gu tschow, Lars Kuerschner, Ulf Neumann, Markus Pietsch, Reik Lo'ser, Norman Koglin, and Kurt Eger., *J. Med. Chem.* 1999, 42, 5437 - 5447.
- [2] Gianfranco Cainelli, Paola Galletti, Spiridione Garbisa, Daria Giacomini, Luigi Sartor and Arianna Quintavalla., *Bioorganic & Medicinal Chemistry.* 2003, 11, 5391 – 5399.
- [3] David E. Zembower, Chin-Min Kam, James C. Powers, and Leon H. Zalkow., *J. Med. Chem.* 1992, 35, 1597 – 1605.
- [4] James B. Doherty, Bonnie M. Ashe, Peter, L. Barker, Thomas J. Blacklock, John W. Butcher, Gilbert O. Chandler, et al., *J. Med Chem.* 1990, 33, 2513 – 2521.
- [5] Chris A. Veale, Peter R. Bernstein, Craig Bryant, Christopher Ceccarelli, James R. Damewood, Jr., et al., *J. Med Chem.* 1995, 38, 98 – 108
- [6] Y Uejima, M Kokubo, J Oshida, H Kawabata, Y Kato and K Fujii., *J Pharmacol Exp Ther.* 1993, 265, 516 – 523
- [7] Zhili Zuo, Xiaomin Luo, Weiliang Zhu, Jianhua Shen, Xu Shen, Hualiang Jiang and Kaixian Chen., *Bioorganic & Medicinal Chemistry.* 2005, 2121- 2131

- [8] J. A. R. P. Sarma, G. Rambabu, K. Srikanth, D. Raveendra and M. Vithal., *Bioorg. Med. Chem. Lett.* 2002, 12, 2689 – 2693
- [9] Jaime N. Delgado and William A. Remers., *Text Book of Organic Medicinal and Pharmaceutical Chemistry Tenth Edition.*
- [10] G. Vinter and Mark Gardner, *Molecular Modelling and Drug Design. First Edition*
- [11] Andrew R. Leach, *Molecular Modelling - Principles and Applications - First Edition.*
- [12] MSI On Library - [www.sinica.edu.tw/~scimeath/msi/index.html](http://www.sinica.edu.tw/~scimeath/msi/index.html)
- [13] G.R. Desiraju, B. Gopalakrishnan, RamK.R. Jetty, DayamRaveendra, Jagarlamudi A.R.P. Sarma and Hosahalli S Subramanya., *Molecules*, 2000, 5, 945 – 955
- [14] Pandi and Veerapandian, Marcel Dekker, *Structure – Based Drug Design*, Inc., Newyork, 1997.
- [15] Dinur, U. Hagler, A.T., *Journal Chem. Phys.*, 1989, 91, 2959 – 2970