Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2017, 9(1):43-53

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

A Predominant Evaluation of Viable Templates for Asthma Therapy Exerting an *In silico* Analog Method, Virtual Library Screening

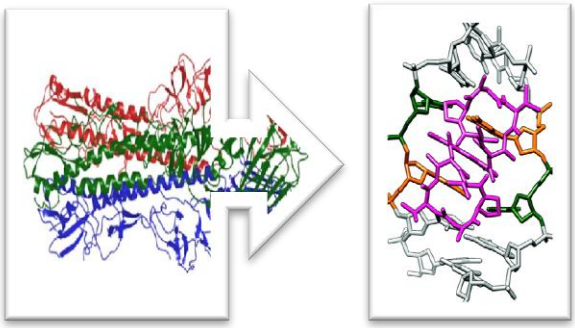
Karpakavalli M[1*], Sangilimuthu AY[2], Sasikala M[3], Komala M[4], Ranjithkumar D[3] and Mohan S[6]

[1]*Department of Pharmaceutical Chemistry, Karpagam College of Pharmacy, Coimbatore, Tamil Nadu, India*
[2]*Deptartment of Biotechnology, Karpagam University, Coimbatore, Tamil Nadu, India*
[3]*Department of Pharmaceutical Analysis, Karpagam College of Pharmacy, Coimbatore, Tamil Nadu, India*
[4]*Deptartment of Pharmaceutics, Mohamed Sathak A.J College of Pharmacy, Chennai, Tamil Nadu, India*
[6]*Department of Pharmaceutical Biotechnology, Karpagam College of Pharmacy, Coimbatore Tamil Nadu, India*

ABSTRACT

Background: A knowledge of the pathology of asthma, a chronic disease of childhood, women and aged personnel and its curative measures have been developed and the rate of morbidity, mortality caused by the disease is at an alarmingly elevated level. Objective: The aim of this project is to focus on the generation of possible templates for the treatment of asthmatic conditions by using an in-silico biological analog method i.e. virtual screening technique following the de-novo ligand based drug design principles so as to synthesize, to analyze and to help decide which compounds to screen experimentally.Method: In this contemporary work, RCSB-PDB data bank -3D protein domains; PROTPARAM-primary structure analysis; SOPMA-seondary structure analysis; CASTp-Protein surface analysis; PROSITE-Motif identification; UNIPROT-Subcellular location; ACCELERY'S DISCOVERY STUDIO 2.1 softwares were used as platforms to perform the protein purification and minimization, docking, active site identification, combinatorial library creation, hydrogen bond screening, ADMETox screening respectively. Results and Conclusion: All these frameworks assist to provide data about the effectiveness of drug-receptor interactions for asthmatic therapy.

GRAPHICAL ABSTRACT



Keywords: Asthma; Templates; *In silico* analog method; Virtual library screening; Combinatorial library compounds; Docking

---

INTRODUCTION

Asthma (Greek, asthma meaning 'panting') is a common chronic inflammatory disease of the airways [1]. A number of other health conditions associated with asthma are gastro-easophageal reflux disease (GERD), rhinosinusitis, obstructive sleep apnea and some psychological disorders [2]. As of 2011, 235-330 million people worldwide are affected by asthma and approximately 2.5-3.45 lakh people die per year from the disease [3]. It is twice more common in boys as girls, in adult women as men and in young than the old [4]. On the basis of mechanism of action, the treatment approaches [5-7] of asthma follows as i) prevention of antigen antibody reaction: avoidance of antigen, hypo-sensitization by antibiotics, ii) inhibition of broncho constriction and mucus, respiratory secretion elevation eg. anti-cholinergics (Tritropium), iii) neutralization of IgE: Omalizumab [8], iv) inhibition of cyclic nucleotide phosphodiesterase (PDEs) enzyme and increase of levels of cAMP and cGMP: eg. methylxanthines, v) suppression of inflammation and hyper reactivity: eg. corticosteroids [9], vi) antagonism of adenosine receptors (action of broncho-constriction and mediator release eg. Theophylline, vii) prevention of release of mediator segment mast cell stabilizers, viii) antagonism of released mediators: eg. anti-histamins, leukotriene and PAF (Platelet aggravating factor) antagonists, ix) blocking of constrictor neurotransmitter eg. sympathomimetics [10], x) β_2 adrenergic receptor agonists (↑ cAMP concentration for broncho-dilation or ↑ conductance of large Ca^{2+} sensitive K^+ channels in airway smooth muscles for membrane hyper-polarization and relaxation) and xi) directly acting bronchodilators eg. methylxanthines [11].

Recombinant DNA derived monoclonal antibody like Omalizumab is not currently used as a first line therapy owing to high cost, limitations on dosage and clinical trial data. Adverse or side effects of some of the marketed anti-asthmatics are mast cell stabilizers, Cromoglycate [12] shows bronchospasm, throat irritation, arthralgia, dysuria, rashes and nasa congestion; Ketotifen [13] shows sedetion, dry mouth and weight gain; Salbutamol's [14] are tremor, drowsiness, fast/slow heart rate, chest pain, muscle cramps, flu symptoms, metabolic acidosis and hypersensitivity; Budesonide [15], a glucocorticoid steroid, shows difficulty breathing, swelling of face behavioral changes, irregular menstrual periods; Montelukast [16], a leukotriene receptor antagonist, gives out gastrointestinal disturbances, sleep disorders, increased bleeding tendency; Corticosteroids [17] show dysphonia, reflex cough and oral candiasis or thrush, adrenal gland suppression, cataracts, glaucoma; Ipratropium [18], an anti-cholinergic drug gives out tachycardia, skin flushing, urinary retention *etc.*,

Many asthma people use unconventional therapy to treat the disease [19]. "Manual therapies" include osteopathic, chiropractic, physiotherapeutic and respiratory therapeutic maneuvers; Acupuncture, usage of vitamin C, buteyko breathing technique which all have no literatures/scientific evidences to treat asthma [20]. A traditional drug development process has resulted in high attrition rates with failures attributed to poor pharmacokinetics (39%), lack of efficacy (30%), animal toxicity (11%), adverse effects in humans (10%) and various commercial and miscellaneous factors [21-22]. Today, the process of drug discovery has been revolutionized with many types of drug design like Structure based (SBDD), Fragment based (FBDD), Ligand based (LBDD), Templates based (MLBDD) and *De-novo* type drug designs (Virtual Library Screening, VLSBDD) and whose applications include Hit identification, Lead demonstration Lead optimization, Bioremediation and Virtual screening for large databases [23-26].

LIPINSKI'S rule of five [27-28] was formulated by Christopher A. Lipinski in 1997 to evaluate drug likeness and describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME). Lipinski's rule says that, in general, an orally active drug has no more than one violation of the following criteria: i) Molecular weight ≤ 300; ii) Number of hydrogen-bond donors ≤ 3; iii) Number of hydrogen-bond acceptors ≤ 3; iv) c logP = 3; v) The number of rotatable bonds was, on average, ≤ 3 and vi) Polar surface area was = 60 Å. The ADMET descriptors [29-30] are given more important as until otherwise the leads would be failing during clinical tests.

Binding between protein and ligands happens by certain moves like translations, rotations and torsional angle rotations (internal changes) in their conformational space, the move which in turn consumes energy and a longer time for evaluation [31-33]. Docking Programs are listed as Dock (I.D. Kuntz, UCSF), Autodock (Arthur Olson, the Scripps research Institute), RosettaDock (Baker, Washington Univ. Gray, Johns Hopkins Univ.) [34-36]. Comparing to high-throughput screening, HTS (physical screening of large libraries of chemicals against a biological target), a new knowledge driven dominant technique known as Virtual Ligand Screening (VLS) is used to do the same screening of large libraries of chemicals for compounds that complement protein targets by computation and to test the predicted most effective binding lead molecules by experimentation [37-39].

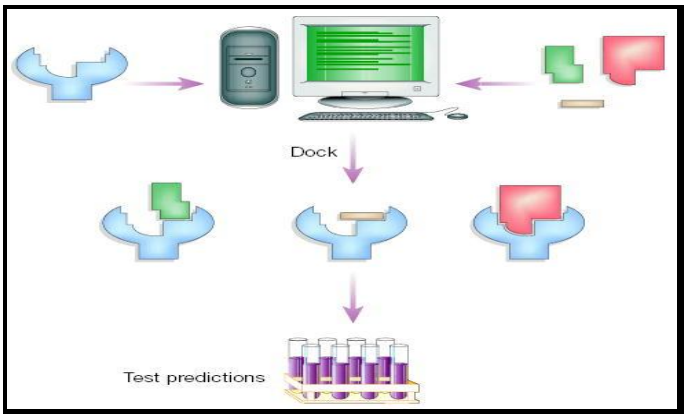


Figure 1: Virtual screening for new ligands (Source: http://blaster.docking.org/zinc/)

Large libraries of available, often purchasable, compounds are docked into the structure of receptor targets by a docking computer program [40-42]. Virtual screening avoids the problem of broad searches of chemical space by restricting itself to libraries of specific, accessible compounds [43], for finding some interesting ligands and to tolerate some false-negatives and is now commonly used in pharmaceutical research [44]. The ligand / template based *in-silico* analog, VLS *de-novo* method involves the identification of active binding sites such as hydrophobic site, hydrogen bonding donor atoms, hydrogen bonding acceptor atoms, polar atoms *etc.*, of the target molecules [45]. These ligands/ templates/ decoy would then be collected to make the combinatorial library [46]. Computer aided library design includes thousands of variations to a fixed template. These libraries cover large areas of chemical and conformational space-molecular diversity in steric, electrostatic, hydrophobic interactions [47]. Many of the literatures, reviews quote and assure the success of the virtual screening technique as a platform to discover a new and worth lead molecules by making use of easy experimental testing and false-positives tolerable data. In the light of the discussed concepts, it is planned to design a few new molecules as templates, if better, as ligands using VLS type CADD technology so as to interact effectively with asthmatic protein targets and to bring forth a new promising lead molecule for asthma [48].

EXPERIMENTAL METHODS

The Research Collaborators for Structural Bioinformatics (RCSB) became accountable for the management of the PDB and is a prime collection of proven structures of proteins, nucleic acids, and complex assemblies. In this ongoing project of VLSB drug design, 15 targeted asthmatic protein domains were scrutinized from PDB database and saved as *.pdb* format. Target characterization was done with all 15 asthmatic target domains using the following softwares.

Primary structure analysis –ProtParam

ProtParam, a Swiss Institute of Bioinformatics- Expasy resource portal, enables the computation of various physico-chemical variables like aliphatic index, instability index, GRAVY (Grand Average Hydropathy), half-life, and isoelectric point (pI) for 15 asthmatic target proteins.

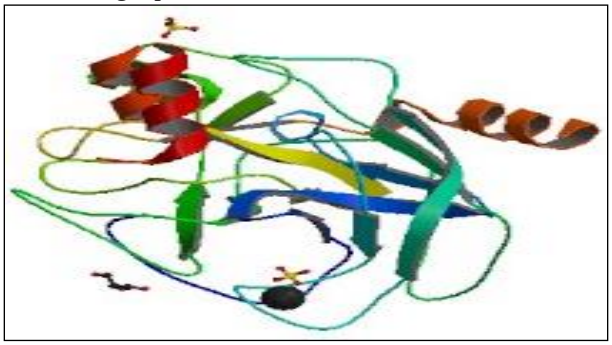
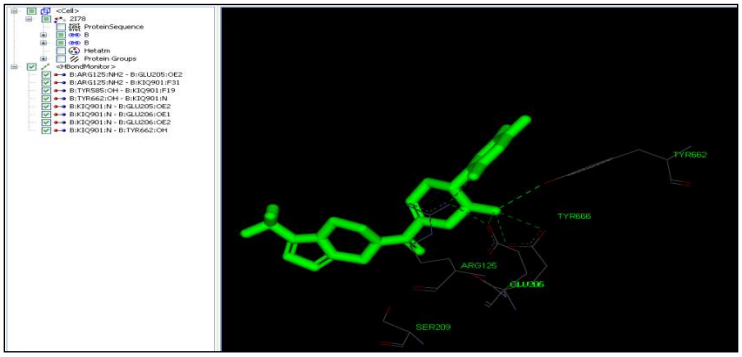


Figure 2: Selected Asthmatic Protein domains and their PDB I.D. with natural ligand

1LOX, 1LOY, 1MWA, 2BNQ, 2EYR, 2EYS, 2EYT, 2Q86,3KXF, 308X,309W, 306F, 3TA3, 3TVM, 3TOE

Figure 3: Target protein's interaction



Aliphatic-index
The aliphatic index of a protein is explicated as the relative volume occupied by aliphatic side chains (alanine, valine, isoleucine, and leucine) and assesed as a positive factor for the increase of thermo stability of globular proteins;

Instability-index
The Instability index is a measure of proteins on the basis of weight values of dipeptides. If the index is less than 40, then it is probably stable in the test tube. If it is inordinate than, it is persumably not stable.

GRAVY (Grand Average of Hydropathy)
The GRAVY value for a peptide or protein is enumerated as the sum of hydropathy values (where both hydrophilic and hydrophobic properties are taken into delibration) of all the amino acids, divided by the number of residues in the sequence. Negative GRAVY value stipulates that the protein is non polar and the positive value is for polar nature.

Iso-electric point [pI]
It is the pH at which the proteins are sturdier.

Half-life
ProtParam connects the half-life of a protein to the congruence of its N-terminal residue which in turn assumes an important role in determining its solidity in in-vivo methods.

Secondary Structure Analysis – SOPMA
SOPMA, a resource portal designated as the self-optimized prediction method from sequence alignment for unerringly predicting the three state description of amino acids (α-helix, ß-sheet and coil) from the amino acid Fasta sequence.

Protein Surface Analysis-CASTp
Computed Atlas of Surface Topography of proteins **(**CASTp**)** contributes for identification and computation of surface accessible pockets as well as interior inaccessible cavities, for proteins, other molecules and measures analytically the area, volume of each cavity.

Motif identification-PROSITE
Prosite, a Swiss Institute of Bioinformatics- ExPASy proteomics analysis server, aids to recount the protein domains, families, motif detection, functional sites, analogous patterns and profiles, which are extracted as targets.

Sub-cellular location-UNIPROT
UNIPROT is a mechanism to anticipate the sub cellular location of the asthmatic proteins by using the fasta sequence input of the accompanying proteins.

Interaction study with natural ligand
Interaction study clarifies the absolute facts about the target's affinity and binding response concerning the ligands.

Protein purification and minimization
The 15 asthmatic proteins were purified using Accelry's discovery studio 2.1 by the subsequent approaches: dismissal of possible conformers; eviction of template/ligand molecules; displacement of hetero atoms; resolution of the missing and incorrectly specified residues and addition of hydrogen atoms to the target proteins. The energy diminution has been accomplished for the asthmatic domains.

Templates from target proteins screening procedure-Evolution method
Recognized pharmacophoric attributes (hydrogen bond donors and acceptors, lipophilic groups, charges) and perceived all molecules in a database that can counterpart it in a low-energy conformation.

ADMETox screening
Eventually, the shortlisted template molecules with less toxic and optimal pharmacokinetic specification were additionally subjected for pharmacophore analysis and screening based on the ADMET properties.

Docking of ligand-target proteins
The filtered new template molecules were issued to endmost docking with the eleven asthmatic protein domains to evaluate the interaction energy. After that, all the identification and characterization of templates along LVSB based drug design technique was concluded.

Steps pursued in Target/Receptor selection and Progression
Some of the most correlated proteins/receptors contemplated for asthmatic studies are Beta-2-microglobulin, DNA polymerase Beta (POLB), Proteosome beta 5 (PSMB5), Beta lactamase, Transforming growth factor (TGF) beta 2 receptor (TGFBR2), Interleukin 2 receptor, H1 receptor. The 3D structure of the receptor which was biologically active and stable downloaded from PDB and computed. The Protein Data Bank (PDB) is storage or conservation of protein crystal structures manifested as complexes with inhibitors. Acquired the asthmatic protein complex from RCSB-PDB and cleaned. All the primary-, secondary- structure analyses, surface screening and motif identification for the selected hits with the stated software were executed. Detached the missing hydrogen or side chain atoms and minimized the complex. Polished the shrank complex and segregated it in macromolecule (protein/receptor referred as lock) and ligand (templates referred as key). Characterized the cavities of proteins and delineated the templates of ligands through virtual library screening, an *in-silico* analogous process. The biggest pocket (real active sites) within the receptor should be pointed out. The receptor may have multiple active sites but one of the new lead molecules of interest should be preferred.

Evolution exerted for pharmacophoric initiation and thorough scrutinization
When once protein was revealed and by determining the criterion for evolution as per Lipinskin's rule of five for pharmacophoric extents, the templates for drug design were discovered. Evolution comprised the connection of all existing templates and might lead to a big drug molecule by subsequent evolutions. Number of evolutions was assumed for starting fragments and refining (dock-1) all of them. Emerged a small molecule employing the fragment library and refined (dock-2 and dock-3 etc.,) the originated complexes until the ensued ligand adhering with the "rule of five" limits. The evolved pilot molecules could be drawn as scaffolds, which do not constrain structural similitude but just demands to peer the pharmacophore. (Alternate: Ligand selection and Preparation Ligands can be derived from diverse databases like ZINC, Pubchem or can be sketched using gadgets like Chemsketch or Chemdraw). Molecular Dynamics simulation was fair for Purification. The feasible generated templates were deposited in a library (combinatorial library). Some screening analysis like ADMETox pharmacokinetic reviews were brought about in order to select a few of the functional templates. The templates were explored with 10 proteins implementing the docking analysis.

Docking

The ligand was docked onto the receptor and the interactions were monitored, rely upon which the appropriate ligands were picked. Protein-ligand docking consisted of two main components which worked consecutively as i) Search algorithm (triggering a large number of poses of a molecule in the binding site) and ii) Scoring function (calibrating a score/binding affinity/strength of binding for a particular pose). Docked all molecules and categorized each by CDOCKER score to notice about the pharmacodynamic variables.

RESULTS

The instability index imparts an estimate of the stability of the protein, protein is stable if instability index <40, and if >40, protein is unstable. Most of the target asthmatic proteins were learnt to have high instability index=42.99 (40-47) owing to the existence of dipeptides. Aliphatic index (signified to assess thermo stability) values fluctuate from 62-72, a comparatively higher values which guaranteed for the thermodynamic stable properties of the contemplated targets in order to combat the higher rate of metabolism. As per the negative value prevailed for GRAVY, it was interpreted that the reviewed asthmatic target proteins were non-polar in nature i.e. hydrophobic. Theoretical pI value ranged between 4.9 and 5.7, a lower acidic value which favours the target proteins to be subsisted in the iso-electronic forms. Sub cellular locations observed for the current receptors were as maximum cytoplasm and cell membrane indicating the hydrophobic behavior of target proteins as a confirmation to the fact of GRAVY findings. Half-life period of all the proteins were detected to be passably emphasizing the kinetic stability of the target proteins and mutational stability of the analogous genes (Table 1). Secondary structure analysis is exercised to express evidently about the bio-functioning of molecules. The tested molecules, when resolved for their secondary structural features (SOPMA), projected some attributes that all these molecules are structurally stabilized by efficient folding technique (Table 2) with comparatively higher percentage of random coil (45-55), α- helix (24-35) and the low percentage of β- turn (4-10). In case, if the percentage of random coil was still higher, we could have envisaged for the best bio-availability strands of the receptors for ligand or molecules interactions. Most of the proteins practised to have abundant cavities due to multifunctional pressures given out by biochemical processes. The protein surface scanning of the targeted asthmatic domains using CASTp disseminated a number of possible pockets scaling from 2661 (Å) to 8873.3 (Å) and area from 1399 (Å) to 4436.9 (Å). 4436.9. Nearly all replicated amino acid sequence in the focused asthmatic receptors became aware by MOTIF and whose sequence, simulation and interacting responses have been evaluated using ACCELERYS STUDIO 2.1 version software.

Table 1: Primary Structure Analysis of the targeted Asthmatic protein domains using PROTPARAM

S No	PDB I.D.	Theoretical pI	Half-Life	Instability Index	Aliphatic Index	Gravy	Sub-Cellular Location
1	1LOX	5.6	20 hrs	42.99	68.28	-0.688	Cytoplasm, cytosol, cell membrane lipid droplets
2	1LOY	5.67	4.4 hrs>20hrs>10hrs	43.75	68.38	-0.689	-
3	1MWA	5.33	4.4 hrs>20hrs>10hrs	44.72	63.81	-0.584	Membrane, single pass membrane protein.
4	3TA3	5.16	7.2 hrs>20hrs>10hrs	45.12	72.79	-0.52	-
5	2BNQ	4.95	Cannot be computed	41.22	63.05	-0.68	Membrane, single pass membrane protein.
6	2EYR	5.09	1 hr; 30mins>10hrs	46.7	62.63	-0.652	Membrane, single pass membrane protein.
7	3TOE	5.54	7.2 hrs>20hrs>10hrs	43.09	67.07	-0.551	Cytoplasm, Chromosomes
8	2EYS	4.96	1 hr; 30mins>10hrs	46.32	63.94	-0.624	Membrane, single pass membrane protein.
9	2EYT	4.94	1 hr; 30mins>10hrs	45.99	63.84	-0.623	Membrane, single pass membrane protein.
10	308X	4.98	1.3hrs;3mins	44.24	66.74	-0.509	-
11	2Q86	5.32	0.8hrs;10mins;10hrs	40.13	67.21	-0.543	Membrane, single pass membrane protein.
12	3KXF	5.04	1.3hrs;3mins	43.18	60.09	-0.771	Membrane, single pass membrane protein.
13	3TVM	5.53	7.2 hrs>20hrs>10hrs	43.25	66.59	-0.571	Cell membrane, single pass type 1cell membrane, endosome membrane, lysosome membrane.
14	309W	5.49	1.9hrs	43.02	66.15	-0.576	Cytoplasm, Nucleus
15	306F	5.49	Cannot be computed	42.72	66.15	-0.58	-

Table 2 - Effective Protein domains selection on the basis of half-life screening

Sl. No.	PDB I.D.	Half-life
1	1LOX	20 hrs
2	1LOY	4.4 hrs>20hrs>10hrs
3	1MWA	4.4 hrs>20hrs>10hrs
4	2EYR	1 hr; 30mins>10hrs
5	2EYS	1 hr; 30mins>10hrs
6	2EYT	1 hr; 30mins>10hrs
7	309W	1.9hrs
8	3TA3	7.2 hrs>20hrs>10hrs
9	3TVM	7.2 hrs>20hrs>10hrs
10	3TOE	7.2 hrs>20hrs>10hrs

Table 3 - Secondary Structure Analysis of the targeted Asthmatic protein domains using SOPMA

Sl. No.	PDB I.D.	Alpha Helix (%)	Extended Strand (%)	Beta Turn (%)	Random Coil (%)
1	1LOY	24.89	31.78	9.32	48.31
2	1MWA	34.55	30.38	5.45	53.47
3	1LOX	24.89	32.77	10.5	45.8
4	2EYR	10.79	29.88	6.22	54.76
5	2EYS	11.52	30.04	5.35	54.76
6	2EYT	11.52	30.04	5.35	54.76
7	309W	27.37	33.33	5.61	48.48
8	3TA3	26.42	32.14	4.23	47.05
9	3TVM	25.91	33.21	9.71	48.48
10	3TOE	21.72	36.81	7.69	44.51

Table 4 - Protein Surface Scanning of the targeted asthmatic protein domains using CASTP

Sl. No.	PDB I.D.	Max. ID	Max. Area	Max. Volume	Min. ID	Min. Area	Min. Volume
1	1LOY	123	3907	8873.3	1	11	5.8
2	1MWA	304	4089.7	7715.7	1	26.3	12.4
3	1LOX	114	3938.4	8682.9	1	25	11.7
4	2EYR	66	1399.1	2661.5	1	25.4	12
5	2EYS	57	2438.2	3857.8	1	25.6	12
6	2EYT	136	2445.2	4840.9	1	31.5	14.1
7	309W	125	2093.4	3530.9	1	27.8	13.5
8	3TA3	120	2165	4292.8	1	31	15.8
9	3TVM	127	2525.2	4901.4	1	18.9	7.5
10	3TOE	202	4436.9	14353	1	14.1	6.7

Table 5 - ADMET values of the Generated Template Molecules with Target Asthmatic Proteins

S N	Name of Templates	Compound		Size & Flexibility				Polarity & Chemical features					
		MF	Mol. Wt.	Atoms/ Bond	Rings	Rotatable bond	Aromatic atoms	C logP	TP SA	H_2 bond acceptor	H_2 bond donor	(-) Ionisable	(+) Ionisable
1	Template 411	$C_{10}H_{10}O_2$	162.18	22/23	2	1	6	1.679	37.3	2	1	0	0
2	Template 457	$C_9H_{12}O_1$	136.19	22/22	1	4	6	2.516	20.23	1	1	0	0
3	Template 570	$C_{10}H_8O_1$	144.17	19/20	2	1	5	2.545	20.23	1	1	0	0
4	Template 896	$C_{10}H_{10}O_2$	162.19	22/23	2	1	10	1.712	37.3	2	1	0	0

Table 6 - Enrichment factors obtained by Evolution studies using LIGANDSCOUT

Sl. No.	PDB I.D.	CDOCKER SCORE			
		411	457	570	896
1	1LOY	22.664	16.975	23.396	23.724
2	1MWA	17.135	21.889	17.261	16.975
3	1LOX	23.545	23.764	22.135	22.889
4	2EYR	21.37	16.705	21.516	23.524
5	309W	20.545	22.631	22.724	21.709
6	3TVM	22.449	23.619	23.724	20.664

Table 7 - CDOCKER Score of the Generated Template Molecules with Target

Sl. No.	Templates	BBB	Absorption	Solubility	Hepatotoxicity	Log P
1	Template 411	2	0	3	0	1.679
2	Template 457	1	0	3	1	2.516
3	Template 570	1	0	4	1	2.545
4	Template 896	1	0	3	0	1.712

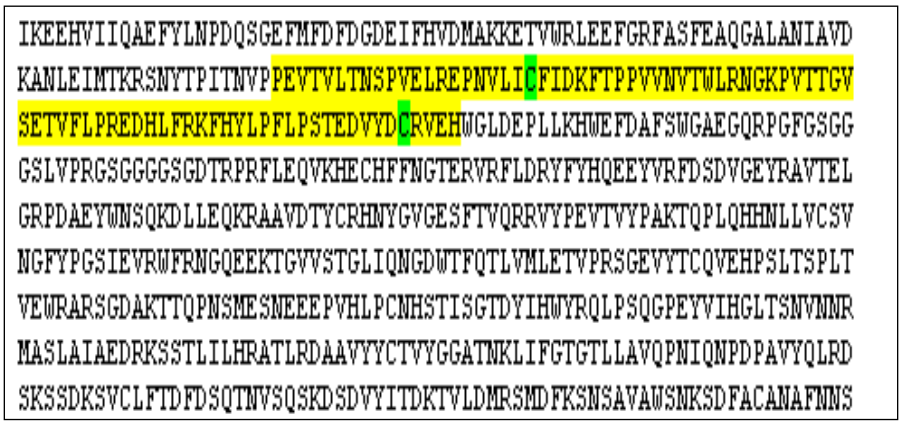


Figure 4: Motif Identification of the targeted asthmatic protein domains using PROSITE
3TOE, 3TA3, 3TVM

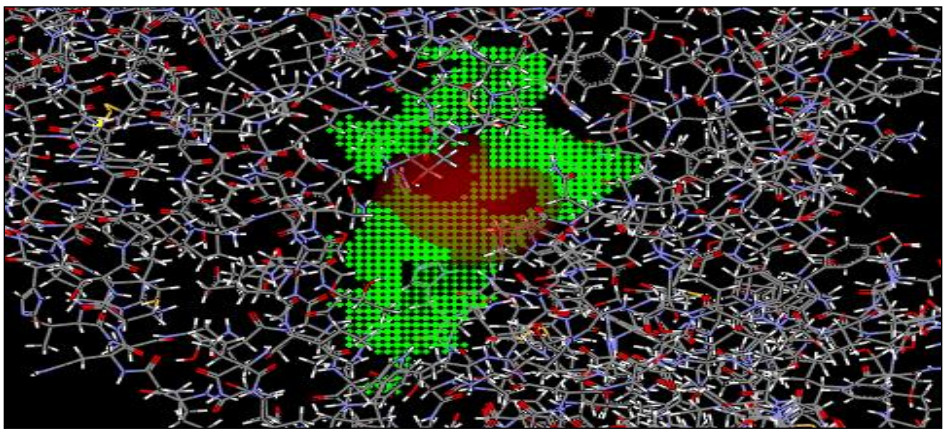


Figure 5: Binding affinity or a score representing the strength of binding of generated templates with target asthmatic proteins using ACCELRYS DISCOVERY STUDIO 2.1

3TVM-07P286

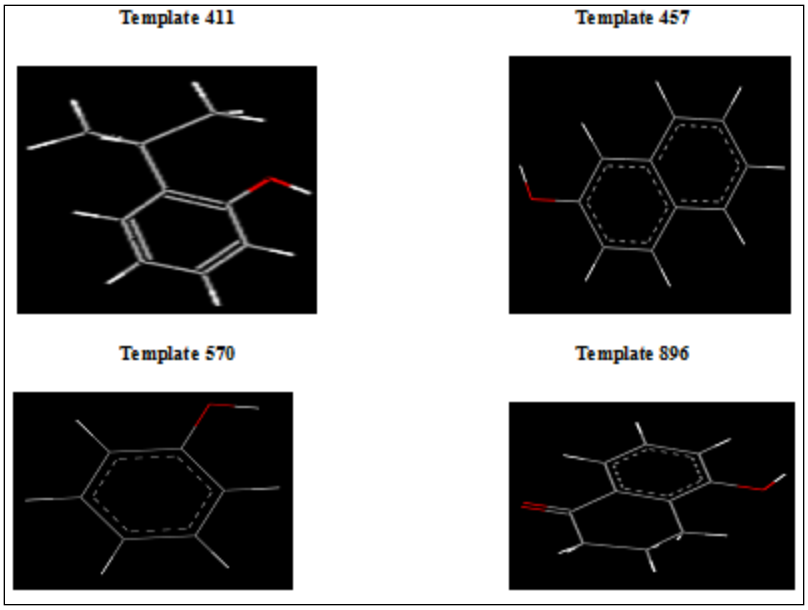


Figure 6: Possible templates predicted from virtual screening using ACCELRYS DISCOVERY STUDIO 2.1

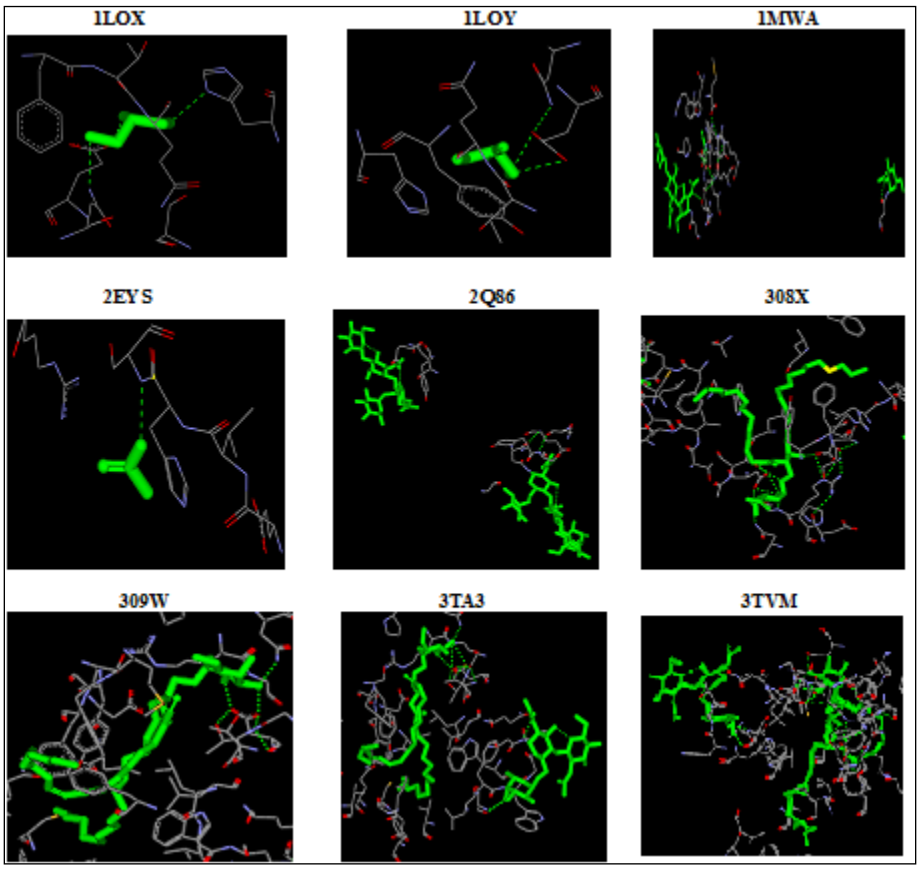


Figure 7: Docking analysis of generated possible templates with target asthmatic proteins using ACCELRYS DISCOVERY STUDIO 2.1

Evolution of ligands within the hotspot of the target has been done to set up the combinatorial library. Evolution carried out by the enrichment factors i.e., the complimentary pharmacophore of hotspot of characterized cavities, helps to design Templates of ligands by LIGANDSCOUT software.

New template or ligand molecule should prolong favorable ADME and solubility. Most of the progressed templates were observed to have the ADMETox values as absorption 0 (good); BBB 1 (high); aqueous solubility 3 (good); hepata-toxicity 0 (non-toxic) and logP values as ≤ 2 which most favorably accepts the benefits of Templates. However, the templates have yet to be evoluted further as their molecular weights and total polar surface area (TPSA) were found to be remarkably lower i.e. (130-160) & (20-37) respectively and the templates have must be stretched to a bigger molecule of ligand so as to achieve molecular weight around 500 and TPSA about 130 ranges through subsequent evolutions and screenings in order to promise for a most effective new molecule. The perceived DECOY (a weak functioning) type templates have to be processed further to get a most practical ligand for the study of Asthma.

Interactional study of the targeted asthmatic protein domains were studied using CDOCKER algotithm. All molecules are interactive and found to be useful. Most of the CDOCKER algorithm findings of the interactions between the targeted asthmatic proteins and the evoluted templates assured for a 'nil' or 'narrow' difference of the CDOCKER energy and the binding energy interpreting their interactions are not hindered by any steric factors. During templates - protein interaction, templates counteract with the target in the most potential conformation facilitating maximum stability to the originated complex.

DISCUSSION

New challenges in synthesis ensue in new analytical methods. In pioneering and instigation, the immeasurable molecules betray along the plan of the time interval between the conception and the approval of a new drug. Novel innumerable greener methods or computational techniques have been vigorously endorsed by drug manufacturers with persistent objective to churn out as several compounds as attainable in search for leads, trusting that the leading the fraction of compounds, the outstanding the liability of reasoning hits.

Molecular docking is to examine about the interaction of two molecules between each other, if so, recognizing the orientation that exploits the interaction and curtails the total energy of the complex. Computer modeling softwares are availed with intent of diminishing the exploration timeframe and cost to refrain the wet lab experiments for decoy elements or no worthy compounds.

To fetch these libraries in docking screens, molecular variables such as protonation, charge, stereochemistry, accessible conformations and solvation must be evaluated. Even conceptual features such as stereochemistry, tautomerization and protonation, are often ambiguous, or can fluctuate on binding to a receptor. This preliminary project work should be achieved for additional evolutions to get a bigger lead molecule judicious for remedial asthma.

CONCLUSION

From the data survey of pharmaco-kinetic and pharmaco-dynamic properties, all the template molecules of concern were realized to be interactive and proficient. This computational exertion optimistically accommodates the unpublished model of templates for the treatment of asthma and might confer ideas/informations/data to the CADD professionals. This modeling of *in-vitro* scrutiny can accordingly be made typical for having them in combinatorial library for asthmatic study and be recycled in succeeding period for further evolution and screening of *in-vitro & in-vivo* clearance. All the templates have been kept in combinatorial library.

ACKNOWLEDGEMENTS

The authors wish to privilege on documentation their heartfelt thanks to the Principal and the management of Karpagam College of Pharmacy, Coimbatore – 641032, Tamil Nadu, India and Dr. Krishnan Nampoothari and CEN groups of Amrita Vishwa Vidhya Peetham, Ettimaddai, and Coimbatore for providing the facilities to accomplish this research work successfully.

REFERENCES

[1] WL Jorgensen. *Sci*, **2004**, 303, 1813-1818.
[2] N Kumar; BS Hendriks; KA Janes;D de Graaf; DA Lauffenburger. *Drug Discov Today*, **2006**, 11, 806-811.
[3] H Kubinyi. Success stories of computer-aided design. In: S Ekins, B Wang. *Computer Appl Pharm Res Dev*. Wiley-Interscience, **2006**, 377-424.
[4] N Claude Cohen. Guidebook on Molecular Modeling in Drug Design Boston. Academic Press, **1996**.
[5] V Vivek; J Anurekha; J Avijeet; G Arun. *Sci Pharm*, **2008**, 76, 333-360.
[6] U Madsen, L Krogsgaard, Liljefors, Tommy. Textbook of Drug Design and Discovery. Washington, DC: Taylor & Francis, **2002**.
[7] DV Green.. *Prog Med Chem*, **2003**, 41, 61-97.
[8] T Hou; X Xu. *Curr Pharm Des*, **2004**, 10, 1011-1033.
[9] G Schneider; U Fechner. *Nat Rev Drug Discov*, **2005**, 4, 649-663.
[10] V Mohan; AC Gibbs; MD Cummings; EP Jaeger; RL Des Jarlais. *Curr Pharm Des*, **2005**, 11, 323-333.
[11] LM Balbes; SW Mascarella; DB Boyd. *Rev Comput Chem*, Lipkowitz and Boyd, Eds; VCH, **1994**: 337.
[12] S Borman. An introduction to *De Novo* techniques in chemical and Engineering News, **1992**, 70: 18.
[13] DV Green. *Prog Med Chem*, **2003**, 41, 61-97.
[14] TI Oprea; H Matter. *Curr Opin Chem Biol*, **2004**, 8, 349-358.
[15] DN Chin; CE Chuaqui; J Singh. *Mini Rev Med Chem*, **2004**, 4(10), 1053-1065.
[16] AN Jain. *Curr Opin Drug Discov Devel*, **2004**, 7, 396-403.
[17] MJ Stoermer. *Med Chem*, **2006**, 2, 89-112.
[18] MD Cummings; RL Des Jarlais; AC Gibbs; V Mohan; EP Jaeger. *J Med Chem*, **2005**, 48, 962-976.
[19] BK Shoichet. *Nat*, **2004**, 432, 862-865.
[20] J Alvarez, B Shoichet. Virtual Screening in Drug Discovery. CRC Press: Boca Raton, FL, **2005**.
[21] T Hou; X Xu. *Curr Pharm Des*, **2004**, 10, 1011-1033.
[22] JM Rollinger. *Curr Med Chem*, **2006**, 13, 1491-1507.
[23] AR Leach; BK Shoichet; CE Peishoff. *J Med Chem.* **2006**, 49(20), 5851-5855.
[24] C Hansch; T Fujita. *J Am Chem Soc*, **1964**, 86, 1616-1626.
[25] National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, **2007**.
[26] RP Ahlquist. *Am J Physiol*, **1948**, 153(3), 586-600
[27] AS Ash; HO Schild. *Br J Pharma Chemother*, **1966**, 27, 427-439.
[28] DI Ball; RT Brittain; RA Coleman; LH Denyer; D Jack; M Johnson; LH Lunts; AT Nials; KE Sheldrick; IF Skidmore. *Br J Pharmacol*, **1991**, 104(3), 665-671.
[29] PJ Barnes. *Eur Respir J*, **2002**, 19(1), 182-191.
[30] PJ Barnes; IM Adcock. *Ann Intern Med*, **2003**, 139, 359-370.
[31] KM Beeh; V Schelfout; F Gronke; F Kanniess; R Cameron; A Vanas. *Proc Amer Thorac Soc*, **2005**, 2, 356.
[32] JJ Curry. *J Clin Invest*, **1946**, 25, 785-791.
[33] JB Howell; RE Altounyan. *Lancet*, **1967**, 2, 539-542.
[34] S Solis-Cohen. *JAMA*, **1900**, 34, 1164-1169.
[35] A Ullman; N Svedmyr. *Thorax*, **1988**, 43(9), 674-678.
[36] LA Rubenstein; RJ Zauhar; RG Lanzara. *J Mol Graph Model*, **2006**, 25, 396-409.
[37] G Fan; E Shumay; H Wang; CC Malbon. *J Biol Chem*, **2001**, 276(26), 24005-24014.
[38] DR Taylor; MA Kennedy. *Am J Pharmacogeno: Genomics Related Res Drug Devel Clin Prac*, **2002**, 1, 165-174.
[39] M Johnson. *Paediatr Respir Rev*, **2001**, 2, 57.
[40] M Johnson. *J Aller Clin Immunol*, **2006**, 117, 18-24.
[41] DW Cockcroft; KY Murdock. *J Aller Clin Immunol*, **1987**, 79, 734-740.
[42] PH *Am Rev Respir Dis*, **1985**, 132(5), 986-992.
[43] OP Twentyman; JP Finnerty; A Harris; J Palmer; ST Holgate. *Lancet*, **1990**, 336, 1338-1342.
[44] AS Rohr; SC Siegel; RM Katz; GS Rachelefsky; SL Spector; R Lanier. *Ann Aller*, **1987**, 59(2), 107-109.
[45] LP Boulet; H Turcotte; S Tennina. *J Aller Clin Immunol*, **1989**, 83(5), 882-887.