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Molecular Docking Studies of MMP25 in Asthma

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Abstract

Matrix metalloproteinase-25 is a protein which is present in humans and it is encoded by MMP25 gene. It is named as leukolysin because it is expressed in leukocytes. It is also expressed by eosinophils, neutrophils, and mast cells. Leukolysin degrades fibronectin, a extracellular matrix component secreted by fibroblast which maintains the form, solidity and integrity of the lungs. As the fibronectin gets cleaved by MMP25, it promotes airway remodeling in asthma due to the altered fibroblast. Hence MMP25 was targeted for the inhibition of airway remodeling. After identification of target, synthetic drug molecules were taken from PubChem database and were evaluated for drug likeliness by using "Lipinski's rule of five" and ADMET properties. In molecular docking studies, aminophylline showed the maximum binding energy with the target protein. Thus *in-silico* method can be a best way to identify best drug lead molecules against MMP25 protein to inhibit airway remodeling.

Keywords: *MMP25, Fibronectin, Lipinski's Rule of Five, ADMET, Molecular docking etc.*

1. Introduction

Matrix metalloproteinase-25 is a protein which is present in humans and it is encoded by MMP25 gene[1,2,3]. It is also a GPI-anchored proteinase and named as leukolysin because it is expressed in leukocyte [4,5]. It is also expressed by eosinophils, neutrophils, and mast cells[6]. Leukolysin degrades extracellular matrix components and promotes airway remodelling[6]. It is expressed in high levels in testis, kidney and skeletal muscle [7]. It cleaves collagen type 4, gelatin, fibronectin and fibrin. Fibronectin is a extracellular component secreted by fibroblast which maintains the form, solidity and integrity of the lungs. As the fibronectin gets cleaved by MMP25, it promotes airway remodeling in asthma due to the altered fibroblast. It does not cleave laminin–1 [8] but it activates the MMP–2 proform [9,10]. It inactivates α1-proteinase inhibitor that reduces proteolytic activity during inflammation[11]. It promotes phagocytosis[12].In Polymorphonuclear Leukocytes(PMNs), MMP25 is stored in the form of granules and it is also detected in the plasma membrane in the lipid rafts[13,14]. MT6-MMP secretion can be regulated by chemokines and cytokines [15]. Thus, MMP25 may play a major role in resolving inflammation by promoting phagocytic removal of neutrophils.

On the basis of action, the treatment for asthma[16-18] are as follows i) bronchial constriction and mucus inhibition eg. anti-cholinergics (Tritropium), ii) IgE neutralization: Omalizumab [19], iii) cyclic nucleotide phosphodiesterase (PDEs) enzyme inhibition and increase of levels of cAMP and cGMP: eg. methylxanthines, iv) suppression of inflammation and hyper reactivity: eg. Corticosteroids [20],v) antagonism of adenosine receptors eg. Theophylline vi) directly acting bronchodilators eg. Methylxanthines [21]. Due to high cost and dosage limitation, Omalizumab is not used for first line therapy. Mast cell stabilizers, Cromoglycate shows adverse side effects such as bronchospasm, throat irritation, rashes and nasa congestion [22]; Salbutamol's [23] shows drowsiness, fast/slow heart rate, chest pain and headache; Budesonide[24] shows breathing problem, swelling of face, behavioral changes, irregular menstrual periods; Montelukast[25] a leukotriene receptor antagonist, shows sleep disorders and increased bleeding tendency; Corticosteroids[26] shows reflex cough, throat and nose irritation, headache; Ipratropium[27], an anti-cholinergic drug shows skin flushing and urinary retention; Methylprednisolone shows high blood pressure, chest pain, vision problems, increased sweating, headache and slow wound healing; anticholinergics shows breathing difficulty, nosebleed, nasal dryness, nasal irritation and dry mouth etc. A traditional drug development process has resulted with failures attributed to poor pharmacokinetics (39%), lack of efficacy (30%), animal toxicity (11%), adverse effects in humans (10%) and various commercial factors[28-29]. Today, the process of drug discovery has been improved with many types of drug design methods like Structure based (SBDD), Ligand based (LBDD),

Templates based (MLBDD) and De-novo type drug designs (Virtual Library Screening) [30-32]. A large number of drugs are already available to prevent the symptoms of asthma but trials are going on to come out with a better drug than the already available one at low cost and with less side effects. Thus, Computer aided drug designing methods offer a wide range of potential drugable ligands to cure asthma that are easy and time- saving and reducing the chances of side effects.

In the present study, we used different *in- silico* tools for identifying a best drug molecule against MMP25 to inhibit airway remodeling. Structure based drug designing has advantage of delivering drug more quickly and at economic cost. Structure based drug designing approaches involves the 3D structure of protein on which docking studies of various small drug molecules are carried out in order to calculate their docking score and binding energy.Virtual screening and molecular docking of the drug molecules on target protein could help to find out the best drug compounds.

2. Materials and Methods

2.1 Homology Modeling and model Validation

The protein sequence of MMP25 was retrieved from the UniProt protein database and then the secondary structure was predicted by using GOR tool. The 3D structure was generated by using SWISS-MODEL server. After modeling, the quality and validation of the model was carried out by Ramachandran plot analysis using PDBsum server. Finally the active site of the protein was predicted by using CASTp (Computed Atlas of Surface Topography of proteins) server.

2.2 Designing of drug library

2D structure of ligand molecules were downloaded from PubChem database in SDF file format [33].

2.3 Virtual Screening by Lipinski's Rule of Five

Drug likeliness properties of ligands were analysed by using Molinspiration server which is mainly based on Lipinski's rule of five. Every ligand molecule should have less than 5 H-bond donor, not more than 10 H-bond acceptor, LogP value not greater than 5 etc. Molinspiration server calculates log P, polar surface area, number of hydrogen bond donors and acceptors, as well as the prediction of bioactivity score [34].

2.4 Virtual Screening by ADMET Properties

The ADMET properties such as Absorption, Distribution, Metabolism, Excreation and Toxicity of the compounds were tested by using AdmetSAR server. AdmetSAR is a freely accessible tool to the public that enables the database to be queried by SMILES and structural similarity search [34].

2.5 Molecular docking studies

Molecular docking is a method that predicts the binding ability between a ligand molecule and the target protein. Molecular docking was carried out by using Vlife MDS (Molecular Dynamics and Simulation) software (version 4.3). All drug compounds were saved in SDF file format and the target protein was saved in PDB file format before subjecting to the software for docking process. [35].Then the docked complex was visualized by using Pymol software for interaction studies.

3. Results and Discussion

3.1 Homology modeling and Validation

PDB id k076 was selected with 43.15% sequence identity. Then the quality and model validation was carried out by Ramachandran plot analysis using PDBsum server. Ramachandran plot analysis indicated that the model were of reliable and good quality as shown in Fig.1. The predicted model was visualized in Rasmol software as shown in Fig.2. Later the predicted model was subjected to CASTp server for active site prediction. Total 135 active sites were predicted in the MMP25 protein.

Table 1: Homology modeling and validation

Parameters	Value
% of identity	43.15%
Template PDB ID	k076
Template Name	2mze.1.A
Validation score	89.40%

PROCHECK statistics

1. Ramachandran Plot statistics

		No. of residues	%-tage
Most favoured regions	[A,B,L]	193	89.4%*
Additional allowed regions	[a,b,l,p]	15	6.9%
Generously allowed regions	[~a,~b,~l,~p]	5	2.3%
Disallowed regions	[XX]	3	1.4%*
Non-glycine and non-proline residues		216	100.0%
End-residues (excl. Gly and Pro)		2	
Glycine residues		26	
Proline residues		22	
Total number of residues		266	

Fig.1: PROCHECK analysis

Fig.2: Visualization of MMP25 protein in Rasmol

3.2 Designing of Drug Library

2D structures of ligand molecules were downloaded from PubChem database. Total 44 drug compounds were downloaded.

3.3 Virtual Screening by Lipinski's Rule of Five

Drug likeliness properties of compounds were predicted by using Molinspiration server which is mainly based on Lipinski's rule of Five. All the drug compounds were tested to Lipinski's rule of five as shown in table 2. In that, the compounds which showed drug likeliness properties were selected for further screening.

3.4 Virtual Screening by ADMET properties

The ADMET (Absorption, Distribution, Metabolism, Excreation and Toxicity) properties of the drug compounds were tested by using admet SAR. Blood-Brain Barrier (BBB) penetration, HIA (Human Intestinal Absorption) and AMES toxicity were calculated. The ADMET properties of drug compounds were shown in Table 3.

3.5 Molecular docking

Molecular docking is a method that predicts the binding ability between a ligand molecule and the target protein. Molecular docking was carried out by using Biopredicta module of Vlife MDS 4.3. Total 35 ligand molecules were docked with MMP25 and the docking score were shown in table 4. As per the table, aminophylline showed better binding energy as compared to other ligand molecules and it was further selected for visualization purpose. The docking score for the complex of aminophylline and MMP25 was found to be -4.580751, concluding the aminophylline was more compatible with the receptor than other ligand molecules. The complex was visualized by using Pymol software and total 6 amino acid residues mainly tyrosine, valine, serine, proline, methionine and glutamine were visualized in the complex (Fig.3).

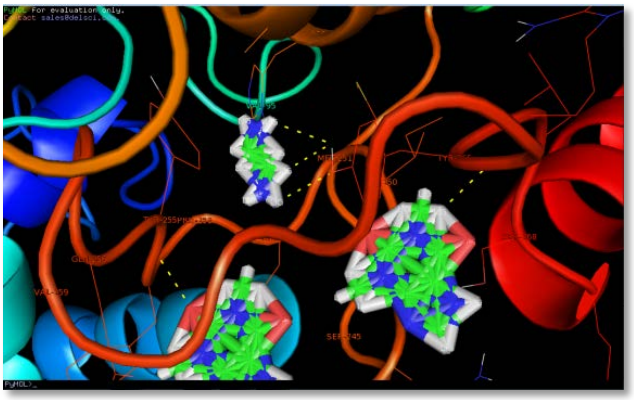

Fig.3: Visualization of docked compound in Pymol software

4. Conclusion

MMP25 was selected for homology modeling and for docking process because it promotes airway modeling of lungs in asthma disease. In the present investigation, aminophylline has came out as a lead drug compound that can be chosen as a successful drug molecule to inhibit the activity of MMP25 which mainly leads to airway remodeling in asthma. Thus, computer aided drug designing method is a best method that can decrease the efforts and time period from lab to field.

Table 2: Virtual screening of ligand molecules by Lipinski's rule of Five.

Sr. No.	Smiles	Mol.wt.	Log P	H bond donor	H bond acceptor	Rotatable bonds
1	CC1CC2C3CCC(C3(CC(C2C4(C1=CC(=O)C=C4)C)O)C)(C(=O)CO)O	374.477	1.9	3	5	2
2	CC12CC(C3C(C1CCC2(C(=O)CO)O)CCC4=CC(=O)C=CC34C)O	360.45	1.6	3	5	2
3	C1=CC=C(C=C1)CCCCOCCCCCCNCC(C2=CC(=C(C=C2)O)CO)O	415.574	3.9	4	5	16
4	CC(CC1=CC=C(C=C1)OC)NCC(C2=CC(=C(C=C2)O)NC=O)O	344.411	1.8	4	5	8
5	CC1CC2C3CC(C4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)SCF)O)C)O)F)C)F	444.509	3.2	2	8	3
6	CCCC1OC2CC3C4CCC5=CC(=O)C=CC5(C4C(CC3(C2(O1)C(=O)CO)C)O)C	430.541	2.5	2	6	4
7	C1=CC2=C(C(=C1)OCC(COC3=CC=CC4=C3C(=O)C=C(O4)C(=O)O)O)C(=O)C=C(O2)C(=O)O	468.37	1.9	3	11	8
8	CCCC1=C2C(=CC3=C1OC(=CC3=O)C(=O)O)C(=O)C=C(N2CC)C(=O)O	371.345	2.2	2	8	5
9	C[N+]1(C2CC(CC1C3C2O3)OC(=O)C(C4=CC=CS4)(C5=CC=CS5)O)C	392.508	2.3	1	6	5
10	CC(C)(C1=CC=CC=C1CCC(C2=CC=CC(=C2)C=CC3=NC4=C(C=CC(=C4)Cl)C=C3)SCC5(CC5)CC(=O)O)O	586.187	7.7	2	5	12
11	CC1=CC=CC=C1S(=O)(=O)NC(=O)C2=CC(=C(C=C2)CC3=CN(C4=C3C=C(C=C4)NC(=O)OC5CCCC5)C)OC	575.68	5.5	2	6	9
12	CC(C1=CC2=CC=CC=C2S1)N(C(=O)N)O	236.289	1.6	2	3	2
13	CN1C2=C(C(=O)N(C1=O)C)NC=N2	180.167	0	1	3	0
14	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CO)O)C)O)Cl)C	408.919	2.2	3	5	2
15	CC1(OC2CC3C4CC(C5=CC(=O)C=CC5(C4C(CC3(C2(O1)C(=O)CO)C)O)C)F)C	434.504	2.5	2	7	2
16	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CCl)O)C)O)Cl)C	427.362	2.7	2	4	2
17	CC(C)(C)NCC(C1=CC(=C(C=C1)O)CO)O	239.315	0.3	4	4	5
18	CC(C)(C)NCC(C1=NC(=C(C=C1)O)CO)O	240.303	-0.1	4	5	5
19	CC(C)(C)NCC(C1=CC(=C(C=C1)O)CO)O	239.315	0.3	4	4	5
20	CC(C)[N+]1(C2CCC1CC(C2)OC(=O)C(CO)C3=CC=CC=C3)C	332.464	2.6	1	3	6
21	CC12CC(=O)C3C(C1CCC2(C(=O)CO)O)CCC4=CC(=O)C=CC34C	358.434	1.5	2	5	2

22	CC1(OC2CC3C4CCC5=CC(=O)C=CC5(C4(C(CC3(C2(O1)C(=O)CO)C)O)F)C)C	434.504	2.5	2	7	2
23	CCC(C(C1=CC(=C(C=C1)O)O)O)NC(C)C	239.315	1.7	4	4	5
24	CCC(=O)OCC(=O)C1(C(CC2C1(CC(C3(C2CCC4=CC(=O)C=CC43C)Cl)O)C)C)OC(=O)CC	521.047	3	1	7	8
25	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CO)O)C)O)F)C	392.467	1.9	3	6	2
26	CCC(=O)OC1(C(CC2C1(CC(C3(C2CC(C4=CC(=O)C=CC43C)F)F)O)C)C)C(=O)SCF	500.573	4	1	9	6
27	CN1C2=C(C(=O)N(C1=O)C)N(C=N2)CC(CO)O	254.246	-1.8	2	5	3
28	CNCC(C1=CC(=C(C=C1)O)O)O	183.207	-1.4	4	4	3
29	CC(C)NCC(C1=CC(=C(C=C1)O)O)O	211.261	-0.6	4	4	4
30	CC1=CC=C(C=C1)C(=O)OC2=C(C=C(C=C2)C(CNC(C)(C)C)O)OC(=O)C3=CC=C(C=C3)C	461.558	5.2	2	6	10
31	CCCN1C2=C(C(=O)NC1=O)NC=N2	194.194	0.3	2	3	2
32	CC1=C(C(=O)C(=C(C1=O)C)C(CCCCCC(=O)O)C2=CC=CC=C2)C	354.446	4.4	1	4	8
33	C1=CC(=C(C=C1C(CNCCCCCCCNCC(C2=CC(=C(C=C2)O)O)O)O)O)O	420.506	1.1	8	8	13
34	C1CN(CCC12CNC(=O)O2)CCC3=CC=CC=C3	260.337	2.1	1	3	3
35	C1=CC=C(C=C1)CCCCOC2=CC=C(C=C2)C(=O)NC3=CC=CC4=C3OC(=CC4=O)C5=NNN=N5	481.512	4.2	2	7	9
36	CCC(C(C1=C2C=CC(=O)NC2=C(C=C1)O)O)NC(C)C	290.363	1.5	4	4	5
37	CC(C)(C)NCC(C1=CC(=C(C(=C1)Cl)N)Cl)O	277.189	2.2	3	3	4
38	CC(C)(C)NCC(C1=CC(=CC(=C1)OC(=O)N(C)C)OC(=O)N(C)C)O	367.446	1.2	2	6	8
Aminophylline	**CN1C2=C(C(=O)N(C1=O)C)NC=N2.CN1C2=C(C(=O)N(C1=O)C)NC=N2.C(CN)N**	**420.434**	**-**	**4**	**8**	**1**
40	CC(C)NCC(C1=CC(=CC(=C1)O)O)O	211.261	0.7	4	4	4
41	CC(CC1=CC=C(C=C1)O)NCC(C2=CC(=CC(=C2)O)O)O	303.358	2	5	5	6
42	CN1C(=C2C(=NC=N2)N(C1=O)C)[O-].C[N+](C)(C)CCO	283.332	-	1	4	2
43	CN1C2=C(C(=O)N(C1=O)C)N(C=N2)CC3OCCO3	266.257	0.9	0	5	2
44	CC(C)C1=NN2C=CC=CC2=C1C(=O)C(C)C	230.311	3	0	2	3

Table 3: Virtual screening of ligand molecules by admet SAR

Sr. No.	Smiles	BBB	CYP450	Carcinogenic	ADMES toxicity
1	CC1CC2C3CCC(C3(CC(C2C4(C1=CC(=O)C=C4)C)O	0.9484	0.8415	Non-carcinogenic	Non ADMES toxic

	)C)(C(=O)CO)O				
2	CC12CC(C3C(C1CCC2(C(=O)CO)O)CCC4=CC(=O)C=CC34C)O	0.9383	0.8496	Non-carcinogenic	Non ADMES toxic
4	CC(CC1=CC=C(C=C1)OC)NCC(C2=CC(=C(C=C2)O)NC=O)O	0.8026	0.7140	Non-carcinogenic	Non ADMES toxic
5	CC1CC2C3CC(C4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)SCF)O)C)O)F)C)F	0.9668	0.8720	Non-carcinogenic	Non ADMES toxic
6	CCCC1OC2CC3C4CCC5=CC(=O)C=CC5(C4C(CC3(C2(O1)C(=O)CO)C)O)C	0.9533	0.8488	Non-carcinogenic	Non ADMES toxic
8	CCCC1=C2C(=CC3=C1OC(=CC3=O)C(=O)O)C(=O)C=C(N2CC)C(=O)O	0.7048	0.8194	Non-carcinogenic	Non ADMES toxic
9	C[N+]1(C2CC(CC1C3C2O3)OC(=O)C(C4=CC=CS4)(C5=CC=CS5)O)C	0.5208	0.6633	Non-carcinogenic	Non ADMES toxic
12	CC(C1=CC2=CC=CC=C2S1)N(C(=O)N)O	0.8846	0.5907	Non-carcinogenic	ADMES toxic
13	CN1C2=C(C(=O)N(C1=O)C)NC=N2	0.9902	0.7738	Non-carcinogenic	Non ADMES toxic
14	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CO)O)C)O)Cl)C	0.9644	0.8456	Non-carcinogenic	Non ADMES toxic
15	CC1(OC2CC3C4CC(C5=CC(=O)C=CC5(C4C(CC3(C2(O1)C(=O)CO)C)O)C)F)C	0.9683	0.8679	Non-carcinogenic	Non ADMES toxic
16	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CCl)O)C)O)Cl)C	0.9721	0.8520	Non-carcinogenic	Non ADMES toxic
17	CC(C)(C)NCC(C1=CC(=C(C=C1)O)CO)O	0.9659	0.7897	Non-carcinogenic	Non ADMES toxic
18	CC(C)(C)NCC(C1=NC(=C(C=C1)O)CO)O	0.9442	0.8123	Non-carcinogenic	Non ADMES toxic
19	CC(C)(C)NCC(C1=CC(=C(C=C1)O)CO)O	0.9659	0.7897	Non-carcinogenic	Non ADMES toxic
20	CC(C)[N+]1(C2CCC1CC(C2)OC(=O)C(CO)C3=CC=CC=C3)C	0.8923	0.7276	Non-carcinogenic	Non ADMES toxic
21	CC12CC(=O)C3C(C1CCC2(C(=O)CO)O)CCC4=CC(=O)C=CC34C	0.9383	0.8496	Non-carcinogenic	Non ADMES toxic
22	CC1(OC2CC3C4CCC5=CC(=O)C=CC5(C4(C(CC3(C2(O1)C(=O)CO)C)O)F)C)C	0.9739	0.8620	Non-carcinogenic	Non ADMES toxic
23	CCC(C(C1=CC(=C(C=C1)O)O)O)NC(C)C	0.9488	0.8052	Non-carcinogenic	Non ADMES toxic
25	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CO)O)C)O)F)C	0.9781	0.8733	Non-carcinogenic	Non ADMES toxic
26	CCC(=O)OC1(C(CC2C1(CC(C3(C2CC(C4=CC(=O)C=CC43C)F)F)O)C)C)C(=O)SCF	0.9701	0.8680	Non-carcinogenic	Non ADMES toxic
27	CN1C2=C(C(=O)N(C1=O)C)N(C=N2)CC(CO)O	0.6357	0.8343	Non-carcinogenic	Non ADMES toxic
28	CNCC(C1=CC(=C(C=C1)O)O)O	0.9660	0.7897	Non-carcinogenic	Non ADMES toxic
29	CC(C)NCC(C1=CC(=C(C=C1)O)O)O	0.9705	0.7778	Non-carcinogenic	Non ADMES toxic
31	CCCN1C2=C(C(=O)NC1=O)NC=N2	0.8963	0.7883	Non-carcinogenic	Non ADMES toxic
32	CC1=C(C(=O)C(=C(C1=O)C)C(CCCCCC(=O)O)C2=CC=CC=C2)C	0.5999	0.7670	Non-carcinogenic	Non ADMES toxic
34	C1CN(CCC12CNC(=O)O2)CCC3=CC=CC=C3	0.9865	0.7942	Non-carcinogenic	Non ADMES toxic
35	C1=CC=C(C=C1)CCCCOC2=CC=C(C=C2)C(=O)NC3=CC=CC4=C3OC(=CC4=O)C5=NNN=N5	0.9446	0.8643	Non-carcinogenic	ADMES toxic
36	CCC(C(C1=C2C=CC(=O)NC2=C(C=C1)O)O)NC(C)C	0.5966	0.8105	Non-carcinogenic	Non ADMES toxic
37	CC(C)(C)NCC(C1=CC(=C(C(=C1)Cl)N)Cl)O	0.8631	0.8142	Non-carcinogenic	Non ADMES toxic
38	CC(C)(C)NCC(C1=CC(=CC(=C1)OC(=O)N(C)C)OC(=O)N(C)C)O	0.7610	0.7745	Non-carcinogenic	Non ADMES toxic
Aminophylline	**CN1C2=C(C(=O)N(C1=O)C)NC=N2.CN1C2=C(C(=O)N(C1=O)C)NC=N2.C(CN)N**	**0.5908**	**0.8073**	**Non-carcinogenic**	**Non ADMES toxic**
40	CC(C)NCC(C1=CC(=CC(=C1)O)O)O	0.9510	0.7750	Non-carcinogenic	Non ADMES toxic
41	CC(CC1=CC=C(C=C1)O)NCC(C2=CC(=CC(=C2)O)O)O	0.9294	0.7004	Non-carcinogenic	Non ADMES toxic
42	CN1C(=C2C(=NC=N2)N(C1=O)C)[O-].C[N+](C)(C)CCO	0.7844	0.7042	Non-carcinogenic	Non ADMES toxic
43	CN1C2=C(C(=O)N(C1=O)C)N(C=N2)CC3OCCO3	0.9387	0.8390	Non-carcinogenic	Non ADMES toxic
44	CC(C)C1=NN2C=CC=CC2=C1C(=O)C(C)C	0.9868	0.8076	Non-carcinogenic	Non ADMES toxic

Table 4: Docking score between ligand molecules and MMP25

Serial Number	Name of the drug	Docking score

1	Methylprednisolone	-3.535342
2	Prednisolone	-3.521577
3	Formoterol	-2.591624
4	Fluticasone	-3.536173
5	Budesonide	-3.377387
6	Nedocromil	-3.325543
7	Tiotropium	-3.120258
8	Beclomethasone	-3.525431
9	Flunisolide	-3.533119
10	Mometasone	-3.534016
11	Albuterol	-3.123001
12	Pirbuterol	-3.125637
13	Levalbuterol	-3.121079
14	Ipratropium	-3.238479
15	Prednisone	-3.516392
16	Triamcinolone acetonide	-3.517842
17	Isoetarine	-3.120934
18	Betamethasone	-3.525982
19	Fluticasone propionate	-2.763501
20	Dyphylline	-3.323042
21	Epinephrine	-3.313774
22	Isoprenaline	-3.124851
23	Enprofylline	-3.513594
24	Seratrodast	-2.549086
25	Fenspiride	-3.328198
26	Procaterol	-3.133771
27	Clenbuterol	-3.316478
28	Bambuterol	-2.541343
29	**Aminophylline**	**-4.580751**
30	Orciprenaline	-3.127099
31	Fenoterol	-2.762235
32	Oxtriphylline	-3.848304
33	Doxofylline	-3.516069
34	Ibudelast	-3.513871
35	Theophylline	-3.520206

References

[1] Pei D (Feb 2000). "Leukolysin/MMP25/MT6-MMP: a novel matrix metalloproteinase specifically expressed in the leukocyte lineage". Cell Res. 9 (4): 291–303. doi:10.1038/sj.cr.7290028. PMID 10628838.

[2] Velasco G, Cal S, Merlos-Suarez A, Ferrando AA, Alvarez S, Nakano A, Arribas J, Lopez-Otin C (Mar 2000). "Human MT6-matrix metalloproteinase: identification, progelatinase A activation, and expression in brain tumors". Cancer Res. 60 (4): 877–82. PMID 10706098.

[3] "Entrez Gene: MMP25 matrix metallopeptidase 25".

[4] Kojima S., Itoh Y., Matsumoto S., Masuho Y.,Seiki M., Membrane-type 6 matrix metalloproteinase (MT6-MMP, MMP-25) is the secong glycosyl-phosphatidyl inositol (GPI)-anchored MMP,FEBS Lett, 2000,480(2–3):142–146.

[5] Pei D., Leukolysin/MMP25/MT6–MMP: a novel matrix metalloproteinase specifically expressed in the leukocyte lineage, Cell Res, 1999, 9(4):291-303.

[6] J.B. Sweet, C. Liebeler, J. Nie, D. Pei, M.N. Blumenthal, "Leukolysin, a potential marker for airway remodeling in asthma", Journal of Allergy andClinical Immunology, Vol. 115, Issue 2, 2005, S69

[7] Bernal F., Hartung H. P., Kieseier B. C., Tissue mRNA expression in rat of newly described matrix metalloproteinases, Biol Res, 2005, 38(2–3):267–271.

[8] English W. R., Velasco G., Stracke J. O., Knäuper V., Murphy G., Catalytic activities of membrane-type 6 matrix metalloproteinase (MMP25), FEBS Lett, 2001, 491(1–2):137–142. Biology of metalloproteinases 333 [32] Velasco G., Cal S.,

[9] Merlos-Suárez A., Ferrando A. A., Alvarez S., Nakano A., Arribas J., López-Otín C., Human MT6–matrix metalloproteinase: identification, progelatinase A activation, and expression in

brain tumors, Cancer Res, 2000, 60(4):877–882.

[10] Nie J., Pei D., Direct activation of pro-matrix metalloproteinase–2 by leukolysin/membrane–type 6 matrix metalloproteinase/matrix metalloproteinase 25 at the asn(109)–Tyr bond, Cancer Res, 2003, 63(20):6758–6762.

[11] Nie J., Pei D., Rapid inactivation of alpha-1-proteinase inhibitor by neutrophil specific leukolysin/membranetype matrix metalloproteinase 6, Exp Cell Res, 2004, 296(2):145–150.

[12] Starr, A. E., Bellac, C. L., Dufour, A., Goebeler, V., Overall, C. M. (2012) Biochemical characterization and N-terminomics analysis of leukolysin, the membrane-type 6 matrix metalloprotease (MMP25): chemokine and vimentin cleavages enhance cell migration and macrophage phagocytic activities. J. Biol. Chem. 287, 13382–13395.

[13] Fortin, C. F., Sohail, A., Sun, Q., McDonald, P. P., Fridman, R., Fulop, T. (2010) MT6-MMP is present in lipid rafts and faces inward in living human PMNs but translocates to the cell surface during neutrophil apoptosis. Int. Immunol. 22, 637–649

[14] Nebl, T., Pestonjamasp, K. N., Leszyk, J. D., Crowley, J. L., Oh, S. W., Luna, E. J. (2002) Proteomic analysis of a detergent-resistant membrane skeleton from neutrophil plasma membranes. J. Biol. Chem. 277, 43399– 43409.

[15] Kang, T., Yi, J., Guo, A., Wang, X., Overall, C. M., Jiang, W., Elde, R., Borregaard, N., Pei, D. (2001) Subcellular distribution and cytokineand chemokine-regulated secretion of leukolysin/MT6-MMP/MMP-25 in neutrophils. J. Biol. Chem. 276, 21960–21968

[16] V Vivek; J Anurekha; J Avijeet; G Arun. Sci Pharm, 2008, 76, 333-360.

[17] U Madsen, L Krogsgaard, Liljefors, Tommy. Textbook of Drug Design and Discovery. Washington, DC: Taylor & Francis, 2002.

[18] DV Green.. Prog Med Chem, 2003, 41, 61-97.

[19] T Hou; X Xu. Curr Pharm Des, 2004, 10, 1011-1033.

[20] G Schneider; U Fechner. Nat Rev Drug Discov, 2005, 4, 649-663.

[21] LM Balbes; SW Mascarella; DB Boyd. Rev Comput Chem, Lipkowitz and Boyd, Eds; VCH, 1994: 337.

[22] S Borman. An introduction to De Novo techniques in chemical and Engineering News, 1992, 70: 18.

[23] TI Oprea; H Matter. Curr Opin Chem Biol, 2004, 8, 349-358.

[24] DN Chin; CE Chuaqui; J Singh. Mini Rev Med Chem, 2004, 4(10), 1053-1065.

[25] AN Jain. Curr Opin Drug Discov Devel, 2004, 7, 396-403.

[26] MJ Stoermer. Med Chem, 2006, 2, 89-112.

[27] MD Cummings; RL Des Jarlais; AC Gibbs; V Mohan; EP Jaeger. J Med Chem, 2005, 48, 962-976.

[28] T Hou; X Xu. Curr Pharm Des, 2004, 10, 1011-1033.

[29] JM Rollinger. Curr Med Chem, 2006, 13, 1491-1507.

[30] 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.

[31] 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.

[32] RP Ahlquist. Am J Physiol, 1948, 153(3), 586-600.

[33] Pubchem-*Kaiser J (May 2005). "Science resources. Chemists want NIH to curtail database."* *Science*.***308***(5723):774*.doi:10.1126/science.308.5723.774a.PMID 15879180.

[34] Sathish Kumar Paramashivam Kalaivani Elayaperumal Boopala bhagavan Natarajan, Manjuladevi Ramamoorthy, Suganthana Balasubramanian & Kannan Narayanan Dhiraviam 2015 Insilico pharmaco-kinetic & molecular docking studies of small molecules derived from Indigo feraaspalathoides Vahl targeting receptor tyrosine Kinases in Bioinformation 11(2):073-084.

[35] Sujit Arun Desai, Santosh Sahedeo Kumbhar, Vishal Shankar Katti, Prafulla Balkrishna Choudhari, Manish Sudesh Bhatia 2013 3D QSAR and Pharmacophore Modelling on Chalcones as Anti- leishmanial Agents potential Trypanothione reductase Inhibitors, Journal of Applied Pharmaceutical Science Vol.3 (12), pp. 099-102.