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Rational drug design of smaller chain peptides as cardioprotective agents: Application towards denovo strategy for drug like properties and docking studies

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ABSTRACT

The main objective of our rational drug design is to predict the best novel shorter chain peptide leads for cardio protective effect from the designed set of templates with various descriptors such as Lipinski rules, molinspiration and swissdock. We built 200 candidate molecules (50 dipeptide,50tripeptide,50 tetrapeptide,50 pentapeptides)and these combination sets were passed through empirical Lipinski filters to assess drug like properties using various molecular descriptors namely molecular mass, hydrogen bond donors, hydrogen bond acceptors, log p(<0.05).The results of Lipinski filters have identified one dipeptide(Leu-Lys),three tripeptides(Ala-Cys-Pro,Gly-Met-Trp,Gly-Trp-Ile)and two tetrapeptides(Ala-Tyr-Phe-Phe,Ala-Cys-Pro-Pro)as potent cardio protective leads. Further ,the selected above 6 peptide leads were subjected to assess drug like properties using molinspiration to check molinspiration property engine,milogp,TPSA,natoms,MW,nviolatios,nrotb,volumerespectively.The results of molinspiration have identified 5 peptide leads with rejection of one tetrapeptide Ala-Tyr-Phe-Phe.In addition ,the same set of leads(5peptides)were subjected to docking with angiotensin converting enzyme target (ACE inhibition)andreceptor target (BETA adrenergic receptor).The calculation of full fitness energy obtained between drug and target receptor/enzyme have shown clearly that the tripeptide Ala-Cys-Pro was more potent with regard to enzyme target having full fitness energy (-538894 k.cal/mol) ,Gly-Trp-Ile was the most potent lead against Beta-adrenergic receptor blockade having full fitness energy of (-231766 k.cal/mol).Moreover the dipeptide Leu-Lys and tripeptide Gly-Met-Trp are also identified as potential targets against both enzyme (ACE) and receptor (BETA-2adrenergic)targets having full fitness energy of (-543953 k.cal/mol) and (-540163 k.cal/mol) against ACE enzyme and (-239715 k.cal/mol) and (-233794 k.cal/mol) against β_2 adrenergic target respectively . So we identified 4 compounds Ala-Cys-Pro, Gly-Trp-Ile, Leu-Lys, Gly-Met-Trp as potent peptide leads with maximum conformational stability for cardioprotective effect among the 200 peptide templates.

Key words: Lipinski rule of five, molinspiration, swissdock, cardio protective peptides, rational drug design

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INTRODUCTION

Lead molecular discovery and development is an expensive and lengthy process for the pharmaceutical industry, the number of years to bring a drug from discovery to market is approximately 14 years, costing up to US$880 million per individual drug .Given the vast size of organic chemical space (>10_{18} compounds),drug discovery cannot be

reduced to a simple "synthesize and test" drudgery. There is an urgent need particularly for life threatening diseases to identify and design lead like molecules from the vast expense of what could be synthesized.

Peptide: Peptides are the short polymers formed from linking, in a definite order, of α-amino acids having Greek meaning –"small digestible". The peptides are shorter than 50 amino acid residues and longer are polypeptides/proteins. Peptides are new cost –effective products based on synthetic peptide strategy. Therapeutic peptides are traditionally derived from natural source, from genetic or recombinant library, from chemical library.

Cardiovascular system*:* The cardiovascular system consists of heart, bloodvessels, and the approximately 5 liters of blood that the blood vessels transport responsible for transporting oxygen, nutrients, hormones and cellular waste products throughout the body, the cardiovascular system is powered by the body's hardest working organ the heart, which is only about the size of closed fist even at rest, the average heart easily pumps over 5 liters of blood throughout the body every minute. Patterns and classification of heart diseases include congestive heart failure, congenital heart disease, ischemic heart disease, hypertensive heart disease, corpulmonale, rheumatic fever and rheumatic heart disease, non-rheumatic endocarditis, valvular diseases and deformities, my ocardial disease, pericardial disease, tumors of the heart, pathology of cardiac interventions.

Angiotensin converting enzyme*:* Angiotensin converting enzyme or "ACE" is a central component of the renin-angiotensin system(RAS),which controls blood pressure by regulating the volume of fluids in the body. It converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. Therefore ACE indirectly increases blood pressure by causing blood vessels to constrict. ACE inhibitors are widely used as pharmaceutical drugs for treatment of cardiovascular diseases. The enzyme was discovered by Leonard T. Skeggs Jr. in 1956.It is located mainly in the capillaries of the lungs but can also be found in endothelial and kidney epithelial cells.

Beta-2 adrenergic receptor*:* (β_2 adrenoreceptor) is a cell membrane spanning beta-adrenergic receptor that interacts (binds) epinephrine, a hormone and neurotransmitter (ligand synonym, adrenaline) whose signaling, via a downstream L-type calcium channel interaction, mediates physiological responses such as smooth muscle relaxation and bronchodilator. Unlike other adrenergic receptors, norepinephrine does not produce β_2 receptor stimulation. The official symbol for the human gene encoding the $\beta_2$adrenoreceptor is ADRB2.Function of beta adrenergic receptor in circulatory system includes heart muscle contraction, increase cardiac output(minor degree compared to β_2),increase heart rate in sinoatrial node(SA node) (chronotropic effect),increase atrial cardiac muscle contractility(inotropic effect),increases contractility and automaticity of ventricular cardiac muscle, dilate hepatic artery, dilate arterioles to skeletal muscle.

OBJECTIVE

Our objective is to identify the suitable peptide lead for cardio protective action based on the rational drug design approach with various strategies, viz, Lipinski rules, mole inspiration and swissdock procedure.

METHODOLOGY

We have selected one of the amino acid in di/tri/tetra/penta peptide based on the past literatures as mandatory in all the combinations and the rest of amino acids in combination was selected as hit and trial approach for the study .totally 200 combinations of the peptides were subjected to Lipinski rule initially. They were as follows, viz., Ala-Gly,Ala-Ser,Ala-Thr,Ala-Val,Ala-Leu,Ala-Ile,Ala-Phe,Ala-Tyr,Ala-Trp,Ala-Pro,Ala-Cys,Ala-Met,Ala-Asp,Ala-Asn,Ala-Glu,Ala-Lys,Ala-His,Ala-Ala,Leu-Gly,Leu-Ala,Leu-Ser,Leu-Thr,Leu-Val,Leu-Leu,Leu-Ile,Leu-Phe,Leu-Tyr,Leu-Trp,Leu-Pro,Leu-Cys,Leu-Met,Leu-Asp,Leu-Asn,Leu-Glu,Leu-Gln,Leu-Arg,Leu-Lys,Leu-His,Gly-Gly,Gly-Ala,Gly-Ser,Gly-Thr,Gly-Val,Gly-Leu,Gly-Ile,Gly-Phe,Gly-Tyr,Gly-Trp,Gly-Pro,Gly-Cys,Ala-Gly-Gly,Ala-Ser-Ala,Ala-Val-Ser,Ala-Val-Thr,Ala-Leu-Val,Ala-Ile-Leu,Ala-Phe-Ile,Ala-Tyr-Phe,Ala-Trp-Tyr,Ala-Pro-Trp,Ala-Cys-Pro,Ala-Met-Cys,Ala-Asp-Met,Ala-Asn-Asp,Ala-Glu-Asn,Ala-Lys-Glu,Ala-His-Gln,Ala-Ala-Arg,Leu-Gly-Lys,Leu-Ala-His,Leu-Ser-Gly,Leu-Thr-Ala,Leu-Val-Ser,Leu-Leu-Thr,Leu-Ile-Val,Leu-Phe-Leu,Leu-Tyr-Ile,Leu-Trp-Phe,Leu-Pro-Tyr,Leu-Cys-Trp,Leu-Met-Pro,Leu-Asp-Cys,Leu-Asn-Met,Leu-Glu-Asp,Leu-Gln-Asn,Leu-Lys-Glu,Leu-His-Gln,Gly-Gly-Arg,Gly-Ala-Lys,Gly-Ser-His,Gly-Thr-Gly,Gly-Val-Ala,Gly-Leu-Ser,Gly-Ile-Thr,Gly-Phe-Val,Gly-Thr-Leu,Gly-Trp-Ile,Gly-Pro-Phe,Gly-Cys-Tyr,Gly-Met-Trp,Ala-Gly-Gly-Gly,Ala-Ser-Ala-Ala,Ala-Val-Ser-Ser,Ala-Val-Thr-Thr,Ala-Leu-Val-Val,Ala-Ile-Leu-Leu,Ala-Phe-Ile-Ile,Ala-Tyr-Phe-Phe,Ala-Trp-Tyr-Tyr,Ala-Pro-Trp-Trp,Ala-Cys-Pro-Pro,Ala-Met-Cys-Cys,Ala-Asp-Met-Met,Ala-Asn-Asp-Asp,Ala-Glu-Asn-Asn,Ala-Lys-Glu-Glu,Ala-His-Glu-Glu,Ala-Ala-Arg-Arg,Leu-Gly-Lys-Lys,Leu-Ala-His-His,Leu-Ser-Gly-

Gly,Leu-Thr-Ala-Ala,Leu-Val-Ser-Ser,Leu-Leu-Thr-Thr,Leu-Ile-Val-Val,Leu-Ile-Val-Leu,Leu-Tyr-Ile-Ile,Leu-Trp-Phe-Phe,Leu-Pro-Tyr-Tyr,Leu-Cys-Trp-Pro,Leu-Met-Pro-Pro,Leu-Asp-Cys-Met,Leu-Asn-Met-Met,Leu-Glu-Asp-Asp,Leu-Glu-Asn-Asn,Leu-Lys-Glu-Glu,Leu-His-Gln-Gln,Gly-Gly-Arg-Arg,Gly-Ala-Lys-Lys,Gly-Ser-His-His,Gly-Thr-Gly-Gly,Gly-Val-Ala-Ala,Gly-Leu-Ser-Ser,Gly-Ile-Thr-Thr,Gly-Phe-Val-Val,Gly-Tyr-Leu-Leu,Gly-Trp-Ile-Ile,Gly-Pro-Phe-Phe,Gly-Cys-Tyr-Tyr,Gly-Met-Trp-Trp,Ala-Gly-Gly-Gly-Gly,Ala-Ser-Ala-Ala-Ala,Ala-Val-Ser-Ser-Ser,Ala-Val-Thr-Thr-Thr,Ala-Leu-Val-Val-Val,Ala-Ile-Leu-Leu-Leu,Ala-Phe-Ile-Ile-Ile,Ala-Tyr-Phe-Phe-Phe,Ala-Trp-Tyr-Tyr-Tyr,Ala-Pro-Trp-Trp-Trp,Ala-Cys-Pro-Pro-Pro,Ala-Met-Cys-Cys-Cys,Ala-Asp-Met-Met-Met,Ala-Asn-Asp-Asp-Asp,Ala-Glu-Asn-Asn-Asn,Ala-Lys-Glu-Glu-Glu,Ala-His-Glu-Gln-Gln,Ala-Ala-Arg-Arg-Arg,Leu-Gly-Lys-Lys-Lys,Leu-Ala-His-His-His,Leu-Ser-Gly-Gly-Gly,Leu-Thr-Ala-Ala-Ala,Leu-Val-Ser-Ser-Ser,Leu-Leu-Thr-Thr-Thr,Leu-Ile-Val-Val-Val,Leu-Ile-Val-Leu-Leu,Leu-Tyr-Ile-Ile-Ile,Leu-Trp-Phe-Phe-Phe,Leu-Pro-Tyr-Tyr-Tyr,Leu-Cys-Trp-Pro-Pro,Leu-Met-Pro-Pro-Pro,Leu-Asp-Cys-Met-Cys,Leu-Asn-Met-Met-Met,Leu-Glu-Asp-Asp-Asp,Leu-Glu-Asn-Asn-Asn,Leu-Lys-Glu-Glu-Glu,Leu-His-Gln-Gln-Gln,Gly-Gly-Arg-Arg-Arg,Gly-Ala-Lys-Lys-Lys,Gly-Ser-His-His-His,Gly-Thr-Gly-Gly-Gly,Gly-Val-Ala-Ala-Ala,Gly-Leu-Ser-Ser-Ser,Gly-Ile-Thr-Thr-Thr,Gly-Phe-Val-Val-Val,Gly-Tyr-Leu-Leu-Leu,Gly-Trp-Ile-Ile-Ile,Gly-Pro-Phe-Phe-Phe,Gly-Cys-Tyr-Tyr-Tyr,Gly-Met-Trp-Trp-Trp.

We built 200 candidate molecules(50 dipeptide,50 tripeptide,50 tetrapeptide,50 pentapeptides) and these combination sets were passed through empirical Lipinski filters to assess drug like properties using various molecular descriptors namely molecular mass, hydrogen bond donors, hydrogen bond acceptors,log p(<0.05).The results of Lipinski filters have identified one dipeptide(Leu-Lys),three tripeptides(Ala-Cys-Pro,Gly-Met-Trp,Gly-Trp-Ile)and two tetrapeptides(Ala-Tyr-Phe-Phe,Ala-Cys-Pro-Pro)as potent cardio protective leads. Further ,the selected above 6 peptide leads were subjected to assess drug like properties using molinspiration to check molinspiration property engine, milogp, TPS A,natoms, MW, nviolatios, nrotb, volume respectively. The results of molinspiration have identified 5 peptide leads with rejection of one tetrapeptide Ala-Tyr-Phe-Phe. In addition ,the same set of leads(5peptides)were subjected to docking with angiotensin converting enzyme target (ACE inhibition)and receptor target (BETA adrenergic receptor).The calculation of full fitness energy obtained between drug and target receptor/enzyme have shown clearly that the tripeptide Ala-Cys-Pro was more potent with regard to enzyme target ,Gly-Trp-Ile was the most potent lead against Beta-adrenergic receptor blockade. Moreover the dipeptide Leu-Lys and tripeptide Gly-Met-Trp are also identified as potential targets against both enzyme (ACE) and receptor (BETA-2adrenergic)targets respectively .so we identified 4 compounds Ala-Cys-Pro,Gly-Trp-Ile,Leu-Lys,Gly-Met-Trp as potent peptide leads with maximum conformational stability for cardio protective effect among the 200 peptide templates.

MATERIALS AND METHODS

- HP Laptop
- Lipinski rules
- Molinspiration
- Swissdock

HP Laptop: Windows 7, processor: Intel (R) core(TM)i3-3110 CPU@2.40G Hz 2.40Hz having installed memory – RAM: 2.00 GB, system type:32-bit operating system.

Lipinski rules:
Its molecular weight is less than 500.The compound's lipophilicity, expressed as a quantity known as log p(the logarithm of the partition coefficient between water and 1-octanol),is less than 5.The number of groups in the molecule that can donate hydrogen atoms to hydrogen bonds(usually the sum of hydroxyl and amine groups in a drug molecule)is less than 5.The number of groups that can accept hydrogen atoms to form hydrogen bonds(estimated by the sum of oxygen and nitrogen atoms)is less than 10.The rules based on the 90-percentilevalues of the drugs property distributions, apply only to absorption by passive diffusion of compounds through cell membranes; compounds that are actively transported through cell membranes by transporter proteins are exceptions to the rule.Rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug inhuman.The rule describes molecular properties important for a drugs pharmacokinetics in the human body including their (Absorption, Distribution, Metabolism, Excretion).However the rule does not predict if a compound is biologically active.

Molinspiration
Molinspiration offers broad range of cheminformatics software tools supporting molecule manipulation and processing including SMILES and SD file conversion ,normalization of molecules ,generation of tautomer's, molecule fragmentation ,calculation of various molecular properties needed in QSAR ,molecular modeling and drug design ,high quality molecule depiction ,molecular database tools supporting substructure and similarity searches .our products support also fragment –based virtual screening ,bioactivity prediction and data visualization. Molinspiration tools are written in java, therefore can be used practically on any computer platform.

Swissdock
Swissdock,a webserver dedicated to the docking of small molecules on target proteins. It is based on the EADock DSS engine, combined with setup scripts for curating common problems and for preparing both the target protein and the ligand input files. An efficient Ajax/HTML interface was designed and implemented so that scientists can easily submit dockings and retrieved the predicted complexes. For automated docking tasks, a programmatic SOAP interface has been set up and template programs can be downloaded in Peri, Python and PHP.

RESULTS AND DISCUSSION

Lipinski rule of five
Variants

- Log p(<5)
- Molecular weight (180-500)
- Hydrogen bond donor(<5)
- Hydrogen bond acceptor(<10)
- Molar refractivity (40-130)

(TABLE 1)-rational drug design of various thermodynamic descriptors of shorter chain peptides by Lipinski rules

S. NO	COMPOUND	LOG P	MOLECULAR WEIGHT	HYDROGEN BOND DONOR	HYDROGEN BOND ACEPTOR	MOLAR REFRACTIVITY
1	A-G	-0.786130	185.00	3	5	47.033092
2	A-S	-1.644340	180.00	6	6	43.777691
3	A-T	-1.290530	187.00	4	6	43.987691
4	A-V	-0.786130	185.00	3	5	47.033092
5	A-L	-0.620030	197.00	3	5	51.556095
6	A-I	-0.620030	197.00	3	5	51.556095
7	A-F	-0.362590	235.00	3	5	61.579090
8	A-Y	0.178690	274.00	3	6	74.649094
9	A-W	-0.562130	187.00	3	5	47.127090
10	A-P	-0.562130	187.00	3	5	47.127090
11	A-C	-1.308830	189.00	3	5	45.728096
12	A-M	-0.671340	216.00	3	5	54.557095
13	A-P	-2.710830	200.00	5	7	45.936497
14	A-N	-2.710830	200.00	5	7	45.936497
15	A-E	-2.832131	216.00	3	7	46.460094
16	A-K	-0.766360	212.00	4	6	54.759792
17	A-H	-1.723230	223.00	4	7	56.452801
18	L-G	-0.786130	185.00	3	5	47.033092
19	L-A	-0.620030	197.00	3	5	51.556095
20	L-S	-1.694631	210.00	3	6	50.940598
21	L-T	-1.135741	225.00	3	6	55.283092
22	L-V	0.160170	225.00	3	5	60.790089
23	L-L	0.326270	237.00	3	5	65.313095
24	L-I	0.326270	237.00	3	5	65.313095
25	L-F	0.359710	273.00	3	5	75.242096
26	L-Y	-0.320290	289.00	4	6	76.403893
27	L-W	0.767610	314.00	3	6	88.406090
28	L-P	0.384170	227.00	3	5	60.884087
29	L-C	-0.362530	229.00	3	5	59.485096
30	L-M	0.274960	256.00	3	5	68.314095
31	L-D	-2.499931	240.00	3	7	55.506096
32	L-N	-0.714561	240.00	5	7	60.854595

33	L-E	-1.885831	256.00	3	7	60.217087
34	L-Q	-1.374431	254.00	5	7	64.310493
35	L-R	-1.253061	280.00	7	8	74.688896
36	L-K	-0.044060	250.00	4	6	68.422798
37	L-H	-0.776930	263.00	4	7	70.209801
38	G-G	-2.122530	131.00	3	5	28.659096
39	G-A	-1.956430	143.00	3	5	33.182098
40	G-S	-3.031030	156.00	3	6	32.566601
41	G-T	-2.472140	171.00	3	6	36.909096
42	G-V	-1.176230	171.00	3	5	42.416096
43	G-L	-1.010130	183.00	3	5	46.939098
44	G-I	-1.010130	183.00	3	5	46.939098
45	G-F	-1.010130	183.00	3	5	46.939098
46	G-Y	-2.472140	171.00	3	6	36.909096
47	G-W	-0.558290	260.00	3	6	69.977097
48	G-P	-0.952230	173.00	3	5	42.510094
49	G-C	-1.698930	175.00	3	5	41.111099
50	A-A	-1.566330	157.00	3	5	37.799095

TRIPEPTIDES

1	A-G-G	-2.240831	204.000	5	7	48.144493
2	A-S-A	-2.983230	241.00	5	8	58.574997
3	A-V-S	-2.203031	269.00	5	8	65.808998
4	A-V-T	-1.644141	284.00	5	8	70.151489
5	A-L-V	-0.182130	296.00	5	7	80.181488
6	A-I-L	0.207970	310.00	5	7	84.798492
7	A-F-I	-0.629150	396.00	6	8	105.724274
8	A-Y-F	-0.629150	396.00	6	8	104.724274
9	A-W-Y	-0.578850	437.00	7	9	118.054962
10	A-P-W	0.493710	375.00	5	8	103.313492
11	A-C-P	-0.038731	391.00	7	9	103.312874
12	A-M-C	-0.809840	319.00	5	7	82.0234491
13	A-D-M	-2.893540	330.00	5	9	77.898499
14	A-N-D	-4.933029	314.00	7	11	69.277901
15	A-E-N	-4.318928	330.00	7	11	73.988899
16	A-K-E	-2.941730	342.00	7	10	82.738892
17	A-H-Q	-2.819929	351.00	8	11	88.598595
18	A-A-R	-2.184060	311.00	8	10	81.156601
19	L-G-K	-0.552461	309.00	6	8	83.291199
20	L-A-H	-1.119231	334.00	6	9	89.601189
21	L-S-G	-2.203031	269.00	5	8	65.808998
22	L-T-A	-1.478041	296.00	5	8	74.674492
23	L-V-S	-1.256731	309.00	5	8	79.565994
24	L-L-T	-0.531741	336.00	5	8	88.431488
25	L-I-V	0.420900	338.00	6	7	93.959175
26	L-F-L	0.963710	384.00	5	7	108.390488
27	L-Y-I	-0.283560	400.00	7	8	109.478981
28	L-W-F	1.047450	461.00	6	8	130.650177
29	L-P-Y	0.341610	390.00	6	8	105.123276
30	L-C-W	0.072339	417.00	6	8	115.744179
31	L-M-P	0.936860	357.00	5	7	97.033478
32	L-D-C	-2.584730	343.00	5	9	82.826492
33	L-N-M	-1.211840	370.00	7	9	95.842896
34	L-E-D	-4.108028	370.00	5	11	83.558487
35	L-Q-N	-2.861228	368.00	9	11	91.839294
36	L-K-E	-1.652160	380.00	6	10	96.475189
37	L-H-Q	-1.873630	391.00	8	11	102.355591
38	G-G-R	-2.740260	285.00	8	10	72.016602
39	G-A-K	-1.722761	267.00	6	8	69.440201
40	G-S-H	-3.530230	293.00	6	10	70.611702
41	G-T-G	-2.980541	230.00	4	8	51.777496
42	G-V-A	-1.518531	242.00	5	7	61.807495
43	G-L-S	-2.427031	267.00	5	8	65.715004
44	G-I-T	-1.076630	284.00	6	8	72.519295
45	G-F-V	-0.538790	318.00	5	7	85.493484
46	G-T-L	-0.828690	348.00	6	8	91.272278

47	G-W-I	0.035210	371.00	5	8	103.180489
48	G-P-F	-0.314790	320.00	5	7	85.587494
49	G-C-Y	-1.741490	338.00	6	8	85.350288
50	G-M-W	-0.016100	390.00	5	8	106.181496

TETRAPEPTIDES

1	A-G-G-G	-2.749229	263.00	7	9	63.012894
2	A-S-A-A	-3.325529	312.00	7	10	75.966400
3	A-V-S-S	-3.619928	353.00	7	11	84.584900
4	A-V-T-T	-1.710639	385.00	8	11	95.731689
5	A-L-V-V	0.255769	395.00	7	9	108.806885
6	A-I-L-L	0.811969	421.00	7	9	117.946884
7	A-F-I-I	0.621409	455.00	7	9	127.781891
8	A-Y-F-F	0.008289	543.00	8	10	149.801804
9	A-W-Y-Y	-1.032811	599.00	8	12	160.908875
10	A-P-W-W	2.193050	560.00	7	11	159.130585
11	A-C-P-P	0.014969	391.00	7	9	103.166870
12	A-M-C-C	-0.894640	422.00	7	9	109.343895
13	A-D-M-M	-2.340850	460.00	7	11	114.047905
14	A-N-D-D	-6.118528	428.00	9	15	93.443100
15	A-E-N-N	-4.769028	444.00	11	15	102.341499
16	A-K-E-E	-4.206557	470.00	8	14	110.770584
17	A-H-E-E	-4.939426	483.00	8	15	112.557587
18	A-A-R-R	-2.801789	465.00	13	15	124.514107
19	L-G-K-K	-0.662060	435.00	10	11	119.570000
20	L-A-H-H	-1.618429	471.00	9	13	127.646294
21	L-S-G-G	-2.711430	328.00	7	10	80.677391
22	L-T-A-A	-1.820340	367.00	4	10	94.065887
23	L-V-S-S	-2.673629	393.00	7	11	98.341896
24	L-L-T-T	-1.389750	435.00	7	11	111.549896
25	L-I-V-V	1.426069	437.00	7	9	122.657875
26	L-I-V-L	1.368170	447.00	7	9	127.086884
27	L-Y-I-I	1.111709	513.00	8	10	142.794785
28	L-W-F-F	1.684890	608.00	8	10	173.727814
29	L-P-Y-Y	-0.469949	552.00	8	11	147.143799
30	L-C-W-P	1.291009	518.00	7	10	144.591995
31	L-M-P-P	1.598760	458.00	7	9	125.752876
32	L-D-C-M	-1.296638	473.00	9	11	123.163300
33	L-N-M-M	-0.311549	500.00	9	11	131.742325
34	L-E-D-D	-6.330227	484.00	7	15	106.899895
35	L-E-N-N	-4.859426	484.00	11	15	115.274696
36	L-K-E-E	-3.036258	512.00	8	14	124.621582
37	L-H-Q-Q	-2.970327	519.00	12	15	134.501450
38	G-G-R-R	-3.357989	439.00	13	15	115.374107
39	G-A-K-K	-1.832360	393.00	10	11	105.719002
40	G-S-H-H	-4.029428	430.00	9	14	108.656799
41	G-T-G-G	-2.697430	291.00	8	10	69.107697
42	G-V-A-A	-1.860830	313.00	7	9	81.198898
43	G-L-S-S	-3.843928	351.00	7	11	84.490898
44	G-I-T-T	-2.726149	381.00	7	11	93.175888
45	G-F-V-V	-0.100891	417.00	7	9	114.118889
46	G-Y-L-L	-1.217690	456.00	7	10	122.107895
47	G-W-I-I	0.505610	484.00	8	10	135.589645
48	G-P-F-F	0.322649	467.00	7	9	128.664871
49	G-C-Y-Y	-2.553051	500.00	8	11	127.370667
50	G-M-W-W	0.671639	578.00	8	11	161.589813

PENTAPEPTIDES

1	A-G-G-G-G	-3.257628	322.00	9	11	77.881294
2	A-S-A-A-A	-3.217728	383.00	9	12	94.312592
3	A-V-S-S-S	-4.843958	439.00	8	14	102.992607
4	A-V-T-T-T	-3.336078	483.00	8	14	116.294594
5	A-L-V-V-V	0.693669	494.00	9	11	137.432358
6	A-I-L-L-L	1.415969	532.00	9	11	151.095459
7	A-F-I-I-I	1.225410	566.00	9	11	160.930527
8	A-Y-F-F-F	-0.151070	687.00	8	12	187.551804

9	A-W-Y-Y-Y	0.788330	761.00	10	15	203.454819
10	A-P-W-W-W	2.984149	749.00	8	14	215.241898
11	A-C-P-P-P	0.563591	492.00	8	11	131.993301
12	A-M-C-C-C	-1.086839	525.00	9	11	136.956375
13	A-D-M-M-M	-1.788158	590.00	9	13	150.197464
14	A-N-D-D-D	-9.377430	542.00	11	19	115.960709
15	A-E-N-N-N	-7.292530	558.00	15	19	129.046524
16	A-K-E-E-E	-5.814656	600.00	10	18	138.823059
17	A-H-E-Q-Q	-5.524728	609.00	14	19	148.796951
18	A-A-R-R-R	-3.777119	619.00	19	20	167.038605
19	L-G-K-K-K	-1.804357	561.00	13	13	153.736282
20	L-A-H-H-H	-1.3015448	616.00	13	17	167.471375
21	L-S-G-G-G	-3.219827	387.00	9	12	95.545784
22	L-T-A-A-A	-2.162638	438.00	9	12	113.457298
23	L-V-S-S-S	-4.090528	477.00	9	14	117.117805
24	L-L-T-T-T	-0.440738	540.00	11	14	139.685944
25	L-I-V-V-V	1.639970	534.00	9	11	151.189453
26	L-I-V-L-L	2.644169	564.00	9	11	160.517502
27	L-Y-I-I-I	1.715710	624.00	10	12	175.943420
28	L-W-F-F-F	2.112659	755.00	10	12	217.565216
29	L-P-Y-Y-Y	0.256490	716.00	12	14	193.601974
30	L-C-W-P-W	2.768209	706.00	9	13	201.443573
31	L-M-P-P-P	2.260660	559.00	9	11	154.472458
32	L-D-C-M-C	-0.106458	630.00	11	13	168.141983
33	L-N-M-M-M	-O.106458	630.00	11	13	168.141983
34	L-E-D-D-D	-8.552428	598.00	9	19	130.241318
35	L-E-N-N-N	-4.993429	597.00	14	19	142.836914
36	L-K-E-E-E	-4.644355	642.00	10	18	152.674164
37	L-H-Q-Q-Q	-4.067028	647.00	16	19	166.647491
38	G-G-R-R-R	-3.975720	593.00	18	20	158.731857
39	G-A-K-K-K	-0.807419	519.00	12	14	142.144516
40	G-S-H-H-H	-4.528627	567.00	12	18	146.702042
41	G-T-G-G-G	-3.205828	350.00	10	12	83.976089
42	G-V-A-A-A	-2.203128	384.00	9	11	100.590294
43	G-L-S-S-S	-5.067958	437.00	8	14	102.898605
44	G-I-T-T-T	-2.768569	483.00	9	14	118.662392
45	G-F-V-V-V	0.337010	516.00	9	11	142.744400
46	G-Y-L-L-L	0.155309	568.00	10	12	157.475311
47	G-W-I-I-I	1.701709	597.00	9	12	169.610580
48	G-P-F-F-F	0.960089	614.00	9	11	171.742538
49	G-C-Y-Y-Y	-1.880310	664.00	12	14	173.974915
50	G-M-W-W-W	2.422179	766.00	9	14	218.414536

Molinspiration

From the results of table 1, we have selected only 6 peptide leads from the 200 peptide templates and further subjected to molinspiration process. The results of molinspiration are expressed in table 2.

(TABLE 2)- molinspirationparameters of shorter chain peptides for its bioactivity

S no	Peptide	Molinspiration bioactivity score	milogp	TPSA	Natoms	MW	noN	NOHNH	Nviolations	Nrotb	volume
1	Leu-lys	2014.11	-2.75	131.20	26	378.41	9	2	0	5	318.73
2	Ala-cys-pro	2014.11	-2.75	131.20	26	378.41	9	2	0	5	318.73
3	Gly-trp-ile	2014.11	1.64	135.14	27	366.38	8	5	0	7	324.22
4	Gly-met-trp	2014.11	0.89	135.14	27	385.43	8	5	0	7	328.32
5	Ala-tyr-phe-phe	2014.11	3.84	168.67	40	538.56	10	6	2	10	477.15
6	Ala-cys-pro-pro	2014.11	-1.56	132.56	26	378.41	9	3	0	5	318.88

As from results of table 2, 5 peptide leads were further selected (leu-lys),(ala-cys-pro),(gly-met-trp),(gly-trp-ile),(ala-cys-pro-pro)and subjected to docking against ACE enzyme and BETA –receptor as biological target using swissdock software .the results of docking for the subjected peptide leads are expressed in table 3

Swissdock

TABLE-3A: full fitness energy score of shorter chain peptide leads by docking against ACE enzyme as drug target.
ACE

S NO	PEPTIDE	CLUSTER	ELEMENT	FULL FITNESS(Kcal/mol)	ESTIMATED DELTA G(Kcal/mol)
1	Ala-cys-pro	4363	924	-538894	-1739.09
2	Leu-lys	770	770	-543953	-1714.36
3	Gly-met-trp	840	840	-540163	-1906.07
4	Ala-cys-pro-pro	805	805	-533127	-1902.02
5	Gly-trp-ile	861	861	-538624	-1844.06

TABLE-3B: full fitness energy score of shorter chain peptide leads by docking against Beta-receptor as drug target.
Beta-adrenergic receptor

S NO	PEPTIDE	CLUSTER	ELEMENT	FULL FITNESS(Kcal/mol)	ESTIMATED DELTA G(Kcal/mol)
1	Gly-met-trp	5285	726	-233794	-1776.79
2	Ala-cys-pro-pro	5253	700	-226755	-1788.43
3	Leu-lys	6730	577	-239715	-1624.67
4	Ala-cys-pro	5861	685	-231271	-1655.98
5	Gly-trp-ile	5850	674	-231766	-1747.85

CONCLUSION

The discovery of new pharmaceuticals via computer modeling is one of the key challenges in modern medicine. Computational methods are anticipated to play a pivotal role in exploiting the structural and functional information to understand specific molecular recognition events of the target peptide molecule with candidate hits leading ultimately to the design of improved leads for the target.In this article ,we sketch a realization of the various stages in the pathway proposed with our own research to demonstrate the way in which an interactive process of computer based rational drug design can aid in developing potent peptides, The results of lipinski filters have identified one dipeptide(Leu-Lys),three tripeptides(Ala-Cys-Pro,Gly-Met-Trp,Gly-Trp-Ile)and two tetrapeptides(Ala-Tyr-Phe-Phe,Ala-Cys-Pro-Pro)as potent cardio protectiveleads. Further ,the selected above 6 peptide leads were subjected to assess drug like properties using molinspiration to check molinspiration property engine, milogp, TPSA, natoms, MW, nviolatios, nrotb, volume respectively. The results of molinspiration have identified 5 peptide leads with rejection of one tetrapeptideAla-Tyr-Phe-Phe. In addition, the same sets of leads (5peptides) were subjected to docking with angiotensin converting enzyme target (ACE inhibition)and receptor target (BETA adrenergic receptor).The calculation of full fitness energy obtained between drug and target receptor/enzyme have shown clearly that the tripeptide Ala-Cys-Pro was more potent with regard to enzyme target having full fitness energy (-538894 k.cal/mol) ,Gly-Trp-Ile was the most potent lead against Beta-adrenergic receptor blockade having full fitness energy of (-231766 k.cal/mol).Moreover the dipeptide Leu-Lys and tripeptide Gly-Met-Trp are also identified as potential targets against both enzyme (ACE) and receptor (BETA-2adrenergic)targets having full fitness energy of (-543953 k.cal/mol) and (-540163 k.cal/mol) against ACE enzyme and (-239715 k.cal/mol) and (-233794 k.cal/mol) against β_2 adrenergic target respectively. So we identified 4 compounds Ala-Cys-Pro,Gly-Trp-Ile,Leu-Lys,Gly-Met-Trp as potent peptide leads with maximum conformational stability for cardio protective effect among the 200 peptide templates.

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REFERENCES

[1] M.Ayoub.,Scheidegger, D., *Chem. Today*,**2006**, .Vol 24, issue 6, pp 46-48.
[2] Davies, J. S., **2003**.*Journal of Peptide Science.* Vol 4, Issue 9, pp 471-501.
[3] Danho, W., Swistok, J., Khan, W., Chu, H., Adrian, C., **2009**.*AdvExp Med Biol.* Vol 2, Issue 611, pp 467-469.
[4] Hughes J,SmithTW,Kosterlitz HW ,Fothergill LA,MorganBA,Morris HR(**1975**)*Nature*,Lond,258,577-579.
[5] Bals, R. & Wilson, J. CMLS, *Cell. Mol. Life Sci*. (**2003**) 60: 711. doi:10.1007/s00018-003-2186-9.
[6] Chien,S,Oeltgen,P.R,Diana,J.N.Shi,X,Nilekani,S.P and salley,R (**1991**) *J Thorac Cardiovascular surg* 107,964-967,oeltgen,P.R Horton,N.D, Boiling S.F,and Su T.P (**1996**) *Ann ThoracSurg* 61,1488-1492.
[7] AM J physiol Heart circ physical **2002** Jun, 282 (6):H 1953-60).Takaratiet.al.

[8] Takakasaki Y, wolffR.A,chienG.L, Van winkle D.M.**1999**, *Am.J.physiol*, 277,442-500.
[9] XiuxinLiu,MartinaLukasova,RadkaZubakova,SabinaLeuicka,ulrichHigenfeldt ,view issue TOC, volume148, issue6, july **2006** ,825-832 ,Heidelberg D69120,Germany.
[10] Danho, W., Swistok, J., Khan, W., Chu, H., Adrian, C., **2009**.*AdvExp Med Biol*. Vol 2, Issue 611, pp 467-469.
[11] BaherahH.Sarmadi,*AminIsmail*,Volume 31,issue10,october **2010** ,1949-1956.
[12] Bellmann, K., Beck, A.G., **2010**.*Trends Pharmacol Sci*. Vol 31, issue 3, pp 434-441.
[13] Lax, R., **2010**.*The International Peptide Review*. Pp 10-15
[14] Kehra, J.P., **1993**.*Crit. Rev. Toxicol.*Vol 6, Issue 23, pp 21-48
[15] Khafagy, S., Morishita, M., **2012**.*Adv Drug Deliv Rev*. vol 2, Issue 64, pp 531-539.
[16] Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (**1997**). *Advanced Drug Delivery Reviews*, 23 (1 ± 3), 3 ± 25.
[17] Falciani, C., Lozzi, L., Pin, A., Bracci, L., **2005**.*Chem. Biol*. Vol 1, Issue 12, Pp 94-98s.
[18] Aure lien grosdidier et al,(**2011**) –swissdock method.
[19] Tux et al,(**2000**) –lipinski rules.
[20] Nojirishuko,Daidahiroyuki,Inaba yutaka,**2004**,Antioxidants and cardiovascular disease.
[21] Li CH,YamashiroD,TsengLF,Loh HH.(**1978**) *International journal of peptide and protein research*.11 (2),154-158.
[22] Lipinski CA,LombardoF,DominyBW,Feeney PJ.(**1997**).*Adv.Drug Del.Rev*.23,3-25.