MOLECULAR DOCKING ANALYSIS OF *NELUMBO NUCIFERA* AND SYNTHETIC COMPOUNDS WITH THE 4KLC / CARDIOVASCULAR DISEASE

A dissertation submitted to

Bishop Heber College (Autonomous), Tiruchirappalli-17.

(Affiliated to Bharathidasan University, Tiruchirappalli-24)

In partial fulfillment of the requirements for the award of the degree of

BACHELOR OF SCIENCE IN BIOINFORMATICS

Submitted by

Y. AARTHI (195824101)

S. BAVITHRA (195824108)

JOY BLESSING SELVARAJ (195824132)

T. KALAIMARAN (195824133)

B. MANIKANDAN (195824137)

R. RADHA (195824145)

Under the guidance of

Dr. M. RAJADURAI

Assistant Professor

Department of Biotechnology & Bioinformatics

Bishop Heber College (Autonomous)

Tiruchirapalli-620017

MAY 2022

DEPARTMENT OF BIOTECHNOLOGY AND BIOINFORMATICS

BISHOP HEBER COLLEGE(AUTONOMOUS)

(Nationally Reaccredited with 'A' grade by NAAC with CGPA of 3.58 out of 4)

(Recognized by UGC as "College of Excellence")

(Affiliated to Bharathidasan University)

Tiruchirappalli-620017

DEPARTMENT OF BIOTECHNOLOGY AND BIOINFORMATICS

BISHOP HEBER COLLEGE(AUTONOMOUS)

(Nationally Reaccredited with 'A' grade by NAAC with CGPA of 3.58 out of 4)

(Recognized by UGC as "College of Excellence")

(Affiliated to Bharathidasan University)

Tiruchirappalli-620017

CERTIFICATE

The Viva-voce examinations for the candidate Y. AARTHI (195824101) S. BAVITHRA (195824108) JOY BLESSING SELVARAJ (195824132) T. KALAIMARAN (195824133) B. MANIKANDAN (195824137) R. RADHA (195824145) was held at Bishop Heber College (Autonomous), Tiruchirappalli on …….....

Examiners:

Internal: Signature ……

Name …….....

External: Signature ……

Name ……

Signature: Head of the Department

DECLARATION

I hereby declare that the dissertation entitled "MOLECULAR DOCKING ANALYSIS OF *NELUMBO NUCIFERA* AND SYNTHETIC COMPOUNDS WITH THE 4KLC / CARDIOVASCULAR DISEASE" submitted to Bishop Heber College (Autonomous) Tiruchirappalli-17, in partial fulfillment of the award of the degree of Bachelor of Science in Bioinformatics is an original work done by me during the period of January 2022 – May 2022 under the guidance of Dr. M. RAJADURAI , Assistant Professor, Department of Biotechnology and Bioinformatics, Bishop Heber College, Trichy-620 001, and has not been included in any other thesis / dissertation submitted for any other degree.

Name of the Candidate :

PLACE:

DATE:

Signature of the candidate

ACKNOWLEDGMENT

First of all, I praise God Almighty for his mercy and blessings throughout my project work. The thesis appears in its current form due to the assistance and guidance of several people. I would like to offer my sincere thanks to all of them.

I would express my heartfelt thanks to Dr. Paul Dhayabaran, Principal, Bishop Heber College (Autonomous) Tiruchirappalli, for his support and blessings

I extend my sincere thanks to Dr.V.VioletDhayabaran, Coordinator, Department of Biotechnology and Bioinformatics,Bishop Heber College(Autonomous) Tiruchirappalli, for her support and her encouraging words to do my project.

My deepest gratitude to Dr. M. Rajadurai, Assistant Professor Department Biotechnology and Bioinformatics, Bishop Heber College(Autonomous) Tiruchirappalli, for his valuable supportand providing all the necessary facilities, resources and guidance for the completion of my project work and at the same time his encouragement and support helped me to overcome many crisis situations to finish this dissertation.

It gives me immense pleasure in thanking, Dr. K. Akila, Associate Professor Dr. D. Rajasudhakar, Ms. A. Sherlin Rosita, Dr. T .Jebastin, Dr. S. Suvai Thenamudhan Assistant Professors Department of Biotechnology and Bioinformatics, Bishop Heber College(Autonomous) Tiruchirappalli for their support and encouragement throughout the project.

I'd like to thank my family and friends who were and will be a constant support in all the endeavors I take in my life.

Y. AARTHI

JOY BLESSING SELVARAJ

S. BAVITHRA

T. KALAIMARAN

B. MANIKANDAN

R. RADHA

CONTEXT

INTRODUCTION

INTRODUCTION

Nelumbo nucifera, an Indian Ayurvedic home grown medication, which gives critical security against cardiovascular diseases. *Nelumbo nucifera* (normal name, lotus), one of two types of the family Nymphaeaceae, has been originated in a few nations, including Egypt, China, India, Japan, and South Korea, and has been utilized for more than 2000 years as a customized medication and dietary part. *Nelumbo nucifera* has become the main restorative plant, and various parts of it, like the bloom, leaf, seed, and rhizome, have been researched for their helpful impacts. Lotus is accounted to curing a few illnesses, including malignant growths, cardiovascular infections, and hepatic sickness. As to cardiovascular illnesses, albeit the restorative impacts of *nelumbo nucifera* rely upon the extraction strategies or the parts utilized for extraction, lotus by and large seems to have mitigating, cancer prevention agent, and hostile to heftiness impacts. For instance, receptaculumNelumbinis (container of *Nelumbo nucifera*.), of which the significant parts are hyperoside, isoquercitrin, quercetin, isorhamnetin, and syringetin, has been accounted for to have serious areas of strength for an action. Be that as it may, dissimilar to different pieces of lotus, just little data is accessible on the impact of receptaculumNelumbinis in cardiovascular illnesses, particularly heart hypertrophy. As unnecessary oxidative pressure is a significant reason for cardiovascular sickness and past reports have shown the cell reinforcement exercises of receptaculumNelumbinis extricate, we guessed that a MeOH concentrate of receptaculumNelumbinis (MRN) may apply a defensive impact on obsessive cardiomyocyte hypertrophy, and along these lines inspected the impact of MRN on intracellular ROS creation and the connected flagging pathways.

Nelumbo nucifera is a huge amphibian rhizomatous spice comprising of slim, lengthened, crawling stem with nodal roots. Lotus is enduring plant with both flying and drifting orbicular leaves. Airborne leaves are cup formed and drifting leaves have level shape. Its petioles are extensively lengthy and unpleasant with unmistakable prickles. Blossoms shift in variety from white to blushing and are agreeably aromatic, lone, and bisexual. Bloom normal breadth is 10-25 cm, and it is ovoid and glabrous. Organic product which consists seeds, are dark in variety, and are hard and ovoid are organized in whorls; seeds aged and were delivered because of twisting down of unit to the water. Tuberous roots are 8 inches long and 2 creeps in breadth. Smooth external skin of the lotus root is green in variety; be that as it may, the inward part has various

huge air pockets running all through the length of the tuber helping for drifting in the oceanic framework.

Assessed the impact of bisbenzylisoquinoline alkaloid isoliensinine segregated from the seed undeveloped organism of *Nelumbo nucifera*, on pneumonic fibrosis actuated by bleomycin in mice. This study exhibited that isoliensinine altogether hindered the hydroxyproline content. Likewise, isoliensinine died down histological injury in lungs due to improving superoxide dismutase (SOD) action and malondialdehyde (MDA) level by bleomycin. Besides, it likewise hinders, cancer corruption factor-(TNF-) α and TGF-β1 overexpression. Comparably proof was given by Zhao et al., 2010, on antifibrosis property of neferine by turning around the decline in SOD movement, expanded in MDA levels and myeloperoxidase action. Neferine likewise reduced bleomycin-prompted increment of TNF-α, interleukin-(IL-) 6, and endothelin-1 in plasma or in tissue. Niu et al., 2013, showed inhibitory impact of neferine on amiodarone-initiated aspiratory fibrosis, because of its strength of against aggravation, hindrance of surfactant protein-D (SP-D), and adjusting of the expanded CD4+CD25+ administrative T cells (Tregs) which might tweak Th1/Th2 lopsidedness by smothering Th2 reaction.

Business makers offer lotus in different measurement structures, including powder, color, dried petals, seeds, and leaves, and mix items in container structure. Lotus root is additionally accessible as a wellbeing drink and food. Corrective plans are additionally accessible. Because of potential medication cooperation, consecrated lotus ought to be utilized carefully by patients being treated for diabetes, elevated cholesterol, mental or heart conditions, or erectile brokenness.

Pharmacologically dynamic constituents have been separated from the seed, leaf, bloom, and rhizome. The synthetic constituents incorporate alkaloids, steroids, triterpenoids, flavonoids, glycosides, and polyphenols, as well as an assortment of minerals.

The seeds are plentiful in protein, amino acids, unsaturated fats, minerals, starch, and tannins. Various alkaloids are the significant auxiliary metabolites in the seeds.A depiction of the compound creation of the seed polysaccharides is additionally available.

N-nornuciferine, O-nornuciferine, nuciferine, and roemerine are the 4 fundamental aporphine alkaloids liable for the pharmacological properties of the plant.Numerous synthetic

investigations archive various alkaloids in the leaves.Several flavonoids are situated in the leaves and stamens; the stamens contain kaempferol and 7 of its glycosides.

The starch in the rhizomes is practically identical to maize and potato starch, with a new rhizome containing 31.2% starch. Nutrient substance incorporates: thiamine (0.22 mg per 100 g), riboflavin (0.6 mg per 100 g), niacin (2.10 mg per 100 g), and ascorbic corrosive (1.5 mg per 100 g). An asparagine-like amino corrosive (2%) has additionally been disengaged in the rhizomes.

Phytochemical studies have shown that the leaf is wealthy in alkaloids, which are viewed as the major bioactive mixtures of the spices. Pharmacological examinations have shown that the alkaloids in the leaves display different organic exercises, including hostile to hyperlipidemia and cholesterol bringing down action, against heftiness, mitigating, and hostile to hyperuricemic impacts.

Most as of late, we observed that the alkaloid part from lotus leaves has narcotic entrancing and anxiolytic impacts by means of restricting to γ-aminobutyric corrosive receptor and enacting the monoaminergic framework. Moreover, NF and N-NF were the two significant alkaloids present in lotus leaves. We theorized that NF and N-NF could cross the blood-cerebrum obstruction. In the wake of concentrating on the tissue appropriation of NF and N-NF in rodents, we found that both were immediately dispersed into the mind, liver, kidney, lung, and heart. What's more, we observed that NF and N-NF can fundamentally hinder the action of the CYP2D6 isoenzyme in a serious way, however the subtleties of the pharmacokinetics of the two mixtures are not known. In spite of the fact that there have been a couple of reports on the pharmacokinetics of NF in the lotus leaf, those on its bioavailability are interesting and inconsistent. A pharmacokinetic concentrate on directed utilizing LC-MS/MS showed that NF was consumed and wiped out rapidly with a high bioavailability of 69.56% after oral organization to rodents, yet another review exhibited that the bioavailability was just 3.9%. Up to this point, different mixtures in the lotus leaves are not known for their pharmacokinetic properties in plasma, particularly in the cerebrum.

Nuciferine (virtue 98%) was bought from the National foundations for Food and Drug Control (Beijing, China). Phenacetin, utilized as an inner norm (IS), was provided by Sigma-Aldrich, Co., LLC. (US). N-NF was secluded from the dried leaves of *Nelumbo nucifera* Gaertn and artificially recognized by correlation of MS, 1H-NMR and 13C-NMR spectra with distributed

information. Its immaculateness was viewed as above 97.8% by HPLC. HPLC-grade acetonitrile was gotten from Fisher Co. Ltd.. Insightful grade triethylamine, methanol and different reagents were acquired from Beijing Chemical Reagent Company. Deionized water was given by a Milli-Q Integral water filtration framework. Counterfeit cerebrospinal liquid (aCSF) was arranged utilizing our recently depicted technique, containing 147 mM NaCl, 4 mM KCl, 0.85 mM MgCl2, and 2.3 mM CaCl2 at pH 7.4.

Cholesterol is a waxy substance found in your blood. Your body needs cholesterol to construct sound cells, however elevated degrees of cholesterol can build your gamble of coronary illness.

With elevated cholesterol, you can foster greasy stores in your veins. At last, these stores develop, making it hard for enough blood to move through your conduits. Here and there, those stores can break abruptly and structure a coagulation that causes a coronary episode or stroke.

Different dietary proteins apply various impacts on plasma cholesterol focuses. Creature studies have shown that creature proteins, most quite casein, increment plasma absolute cholesterol focuses contrasted and vegetable proteins, like soy. Soy protein has been demonstrated to be hypocholesterolemic in rodents, pig, primates, and hares. Epidemiologic investigations have unveiled that veggie lovers have lower mean plasma cholesterol focuses than populaces consuming weight control plans of blended proteins, yet it is indistinct whether this impact results explicitly from the creature or vegetable nature of the protein. In human clinical examinations, subbing soy protein for blended protein lessens plasma all out cholesterol focus in hypercholesterolemic subjects, however it causes just a little, nonsignificant change in people with ordinary plasma cholesterol fixations. The system answerable for the impacts of various proteins on plasma cholesterol fixations has not been laid out. One speculation recommends that creature proteins, which have a more noteworthy substance of phosphorylated amino acids than vegetable proteins, disrupt bile corrosive reabsorption. Another theory recommends that the amino corrosive substance of the protein influences cholesterol assimilation, tissue capacity, combination, and discharge. The dietary protein may likewise adjust cholesterol digestion by influencing plasma chemical fixations, either postprandially or over weeks to months. Among the chemicals remembered to be impacted by dietary protein source are insulin, glucagon, and thyroid chemicals.

Gastrointestinal chemicals, like gastrointestinal inhibitory polypeptide, may likewise be impacted by dietary protein.

4KLC E343D/F110A Double mutant of human ferrochelataseis the protein responsible for LDL cholesterol. LDL (low-density lipoprotein), once in a while called "bad" cholesterol, makes up the greater part of your body's cholesterol. Elevated degrees of LDL cholesterol raise your gamble for coronary illness and stroke.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is related with autosomal predominant hypercholesterolemia, a condition of raised degrees of LDL (low-thickness lipoprotein) cholesterol. Autosomal prevailing hypercholesterolemia can bring about extreme ramifications like stroke and coronary illness. The restraint of PCSK9 work by remedial antibodies that block communication of PCSK9 with the epidermal development factor-like recurrent A space of LDL receptor (LDLR) was displayed to effectively bring down LDL cholesterol levels in clinical investigations. Here we present information on the recognizable proof, underlying and biophysical portrayal and in vitro and in vivo pharmacology of a PCSK9 immune response (mAb1). The X-beam structure shows that mAb1 ties the module 1 of the C-terminal space (CTD) of PCSK9. It blocks admittance to a region bearing a few normally happening gain-of-capacity and loss-of-work changes. Albeit the immune response doesn't hinder restricting of PCSK9 to epidermal development factor-like rehash A, it to some degree switches PCSK9-instigated decrease of the LDLR and LDL cholesterol take-up in a cell measure. mAb1 is likewise compelling in bringing down serum levels of LDL cholesterol in cynomolgus monkeys in vivo. Complete deficiency of PCSK9 is related with inadequate liver recovery and expanded chance of hepatitis C contaminations. Impeding of the CTD is adequate to somewhat repress PCSK9 work. Antibodies restricting the CTD of PCSK9 may accordingly be profitable in patients that don't endure total hindrance of PCSK9.

Whenever your body has a lot of LDL cholesterol, the LDL cholesterol can develop on the walls of your veins. This development is classified "plaque." As your veins develop plaque over the long run, the internal parts of the vessels thin. This restricting squares blood stream to and from your heart and different organs. Whenever blood stream to the heart is obstructed, it can cause angina (chest torment) or a respiratory failure.

OBJECTIVES OF PRESENT STUDIES

OBJECTIVES OF PRESENT STUDIES

- The main objective in the molecular docking problem is to find an optimized conformation between the ligand (table 1) and the receptor (*4KLC*) from the GCMS extracted compounds of *Nelumbo nucifera*' s carpellary receptacle.
- The molecular docking of the multitude of tests was done to get a superior comprehension of themethod to communicate between the ligands and individual designated proteins and to follow their limitingpores and refers to it.
- This docking studies helps in finding newer and efficient drugs.

REVIEW OF LITERATURE

REVIEW OF LTERATURE

Rho-kinase 1 (ROCK1) is a vital sub-atomic objective for controlling smooth muscle (SM) compression in asthma, gastrointestinal problems, hypertension. Incipient organisms of lotus seed (*Nelumbo nucifera*) are conventional people spices generally utilized in treating different illnesses which are firmly connected with SM constriction. Fully intent on making sense of the component of undeveloped organisms of lotus seed, 27 isoquinoline alkaloids were detached from the incipient organisms of lotus seed, the inhibitory action of these alkaloids against ROCK1 were virtual screened by means of sub-atomic docking and sub-atomic elements (MD) reproductions. The docking results showed that 5 bisbenzylisoquinolines (BBIs) and 1 tribenzylisoquinoline (TBI) were strong inhibitors with high restricting partiality for both An and B chains of ROCK1 (AcRock and BcRock). The MD results likewise uncovered that neoliensinine was the most intense inhibitor, which was comparing to the irreversible unwinding impact of neoliensinine on SM. Additionally, through the MD reenactment, it likewise demonstrated that neoliensinine connected in its extended conformity through polar solvation associations and van der Waal powers. At long last, with the best estimation results, the restraint impact of neoliensinine on the withdrawal of vascular smooth muscle cells (VSMCs) and ROCK1 was additionally affirmed by a few organic tests. Confirmed by Jian Liu et al (2019).

In this work, an effortless system in view of ligand fishing was created to separate and recognize lipase inhibitors present in lotus leaves. Profoundly steady and dynamic lipase-Fe3O4 superparamagnetic nanoparticle forms (LMNPs) were ready and utilized as lures. Two flavonoids in lotus leaf extricate were found to tie to the snares and were distinguished as quercetin-3-O-β-d-arabinopyranosyl-(1→2)- β-d-galactopyranoside (1) and quercetin-3-O-β-d-glucuronide (4) in view of electrospray ionization-mass spectrometric investigations. Their half inhibitory focuses on lipase (IC50) were 52.9 ± 3.2 and 17.1 ± 1.5 μg/mL, individually. What's more, they were found to essentially extinguish the fluorescence of lipase, proposing major areas of strength for them with this catalyst, which was additionally proven by atomic docking. Ligand fishing in view of LMNPs shows extraordinary power for quick screening and recognizable proof of lipase inhibitors present in consumable and therapeutic plants. Reported by Yuvan-Ting Zhu et.al (2014).

Atsuko Itoh et.al analysed that From the undeveloped organisms of the seeds of *Nelumbo nucifera*, three bisbenzylisoquinoline alkaloids, nelumboferine and nelumborines An and B, were confined alongside four known compounds, neferine, liensinine, isoliensinine and anisic corrosive. The designs of the new alkaloids were resolved chiefly by spectroscopic techniques

Ghazali et.al(2017) investigated that few investigations have uncovered that flavonoids from *Nelumbo nucifera* leaves extricate showed pancreatic lipase-inhibitory action. In this study flavonoids from N. nucifera in particular leucoanthocyadin, rutin and astragalin were decided to go through sub-atomic docking investigation utilizing AutoDock 4.2. Sub-atomic docking is an in silico strategy to foresee the limiting site of the chose compounds towards pancreatic lipase structure. Docking reproduction uncovered that astragalin showed the best proclivity towards pancreatic lipase when contrasted with the other two flavonoids. Astragalin delivered more hydrogen bonds and had lower free restricting energy contrasted with orlistat. Additionally, astragalin shaped solid hydrogen bond with key amino corrosive Ser 152 in the reactant set of three and showed great ligand acknowledgment as it likewise had solid hydrogen bond with His 151, Phe 215 and Arg 256. This starter in silico result recommends that astragalin could go about as an enemy of stoutness specialist through pancreatic lipase hindrance activity

Rajendran Harishkumar et.al(16may2021) investigated the cardioprotective job of the methanolic leaf concentrate of *Nelumbo nucifera* and nuciferine against isoproterenol-actuated myocardial dead tissue (MI) in Wistar rodents. Pretreatment with leaf remove and nuciferine (200 and 20 mg/kg body weight, individually) against MI initiated by isoproterenol (85 mg/kg body weight) fundamentally diminished heart weight; levels of cardiovascular markers, for example, lactate dehydrogenase and creatine kinase-MB were like those in controls. The treatment fundamentally expanded the substance of endogenous cancer prevention agents and diminished lipid peroxidation in completely treated gatherings. Treated bunches showed a critical decrease in pulses each moment as contrasted and the MI-prompted positive control. The MI-prompted bunch showed neurotic ramifications like tachycardia, left atrial expansion, and anterolateral ST-raised MI, which were missing in treated gatherings. Histology affirmed that the leaf separate and nuciferine forestalled primary irregularity and irritation in heart and liver tissues of treated gatherings. On in silico examination, nuciferine showed more grounded restricting connection with both β1 and β2

adrenergic receptors than isoproterenol. Subsequently, the leaf concentrate of N. nucifera and nuciferine could be utilized as plant-based cardioprotective specialists

Jingfang Li (15may2021)found that Lotus seeds are exceptionally vulnerable to carmelizing in light of the catalysis of polyphenol oxidase (PPO), which caused a huge misuse of lotus assets, so it is critical to explore the PPO in lotus seeds. In this review, lotus seed PPO was slowly decontaminated with 26.92 times crease and a 1.43% yield. The atomic load of lotus seed PPO was tried at 58 kDa, and its three-layered (3D) model comprised of eight α-helices, ten β-sheets, and arbitrary curls. A sum of 14 phenolic compounds were recognized in lotus seeds. Nonetheless, lotus seed PPO showed different fondness towards these phenolic substrates. Indeed, even the stereoisomers, (+)- catechin and (−)- epicatechin, showed unique Km and Vmax values. In this way, the reactant system among PPO and these stereoisomeric substrates was investigated utilizing near sub-atomic docking. As opposed to (+)- catechin, (−)- epicatechin framed more Pi-Alkyl associations and hydrogen bonds with amino corrosive deposits in the hydrophobic pocket of PPO. (−)- Epicatechin had a lower HOMO-LUMO energy hole and higher atomic ovality subsequent to entering the dynamic pocket of PPO than (+)- catechin. To close, the reactant instrument of lotus seed PPO was explained by similar sub-atomic docking studies, and (−)- epicatechin was proven as the ideal substrate of lotus seed PPO.

MATERIALS AND METHODS

MATERIAL AND METHODS

The GCMS of *Nelumbo nucifera* is collected from the journals, (Journal of Life Science. 2016. Oct, 26(10): 1196-1201 DOI : http://dx.doi.org/10.5352/JLS.2016.26.10.1196, Gahee Ryu, Jin Bae Weon, Woo Seung Yang, Choong Je Ma, "Simultaneous Determination of Four Compounds in a *Nelumbo nucifera* Seed Embryo by HPLC-DAD", Journal of Spectroscopy, vol. 2017, Article ID 6426394, 6 pages, 2017. https://doi.org/10.1155/2017/6426394, Journal of Applied Pharmaceutical Science Vol. 5 (04), pp. 115-118, April, 2015 Available online at http://www.japsonline.com DOI: 10.7324/JAPS.2015.50419, Journal of Academia and Industrial Research (JAIR) Volume 4, Issue 12 May 2016.)

In the current study, all the compounds that showed good binding affinity, also exhibited drug like characteristics based on Lipinski's rule of 5 that determines if the compound, has certain pharmacological or biological activity to make it an orally active drug in humans. The molecular weights of all the compounds are below 500 Daltons, with less than 5 hydrogen bond donors and 10 hydrogen bond acceptors. In addition, analysis of pharmacokinetic properties such as the partition coefficient and Water solubility (QPlogS) of the evaluated compounds are within the range. The top 5 compounds also showed good cell permeability (QPlogKhsa), bioavailability (QPCaco, QPMDCK) and high serum protein binding capacity (QPlogBB). All the pharmacokinetic parameters are within the acceptable range defined for human use, which collectively indicated that the screened compounds could be taken forward, for further analysis.

4KLC Protein

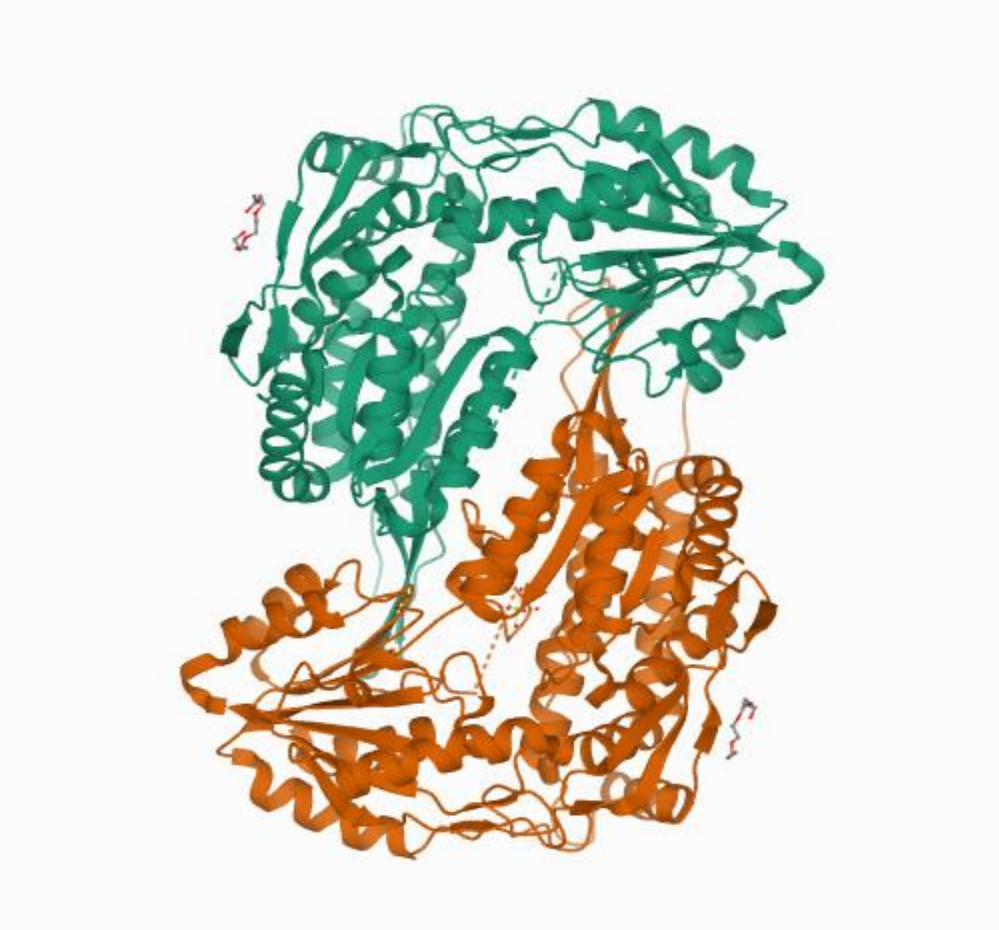


Fig 01 : 3D Image of 4KLC Protein

The designs of proteins utilized in this work were downloaded from the Protein Data Bank.The itemized data of the chose proteins, their PDB IDs, inbuilt inhibitor, X-beam goal,and so forth, were yielded. Sub-atomic docking concentrate on has been done by the Glide dockingprogram given by Schrodinger suite. Protein arrangement is finished by utilizing the Protein arrangement Wizard module of Glide. At first, all the protein structures should be preprocessedto be utilized as a receptor for docking. A portion of the commonplace activities in preprocessing incorporate (I)expansion of hydrogen molecules, (ii) task of nuclear charges, and (iii) end of wateratoms that are not associated with ligand restricting

These compounds are further docked with the target protein (4KLC) using Schrödinger (maestro).

The ligands from various information bases (Pubchem) were downloaded. Schrodinger ligand planning item, Ligprep was utilized to get ready superior grade, all iota 3D designs. The ligand planning included 2D-3D transformations, producing varieties, revision, confirmation and advancement of the designs. Receptor lattice was produced involving Receptor network age in the Glide application (Glide, variant 5.8, Schrödinger, LLC, and New York-2) of Maestro (Schrödinger, LLC, New York, NY, 2014-2). The receptor lattice for NEK2 was produced by indicating the limiting (dynamic) site deposits, which was recognized by SiteMap apparatus. When the receptor framework is produced, the ligands are docked to the protein (NEK2) utilizing Glide form 5.8 (Grid based LIgand Docking with Energetics) docking convention. The ligands were docked utilizing "Additional accuracy mode" (XP). The docked conformers were assessed utilizing Glide (G) Score. The G Score is determined as follows:

G Score = a*vdW+b*Coul + Lipo + Hbond + Metal + BuryP + RotB + Site

Wherein vdW means van der Waals energy, Coul signifies Coulomb energy, Lipo means lipophilic contact, HBond shows hydrogen-holding, Metal demonstrates metal-restricting, BuryP shows punishment for covered polar gatherings, RotB shows punishment for freezing rotatable

securities, Site indicates polar communications in the dynamic site and the a=0.065 and b=0.130 are coefficients of vdW and Coul.

RESULT AND DISCUSSION

RESULT AND DISCUSSION

Phytocomponents identified in ethanolic extract of *Nelumbo nucifera* by GCMS.

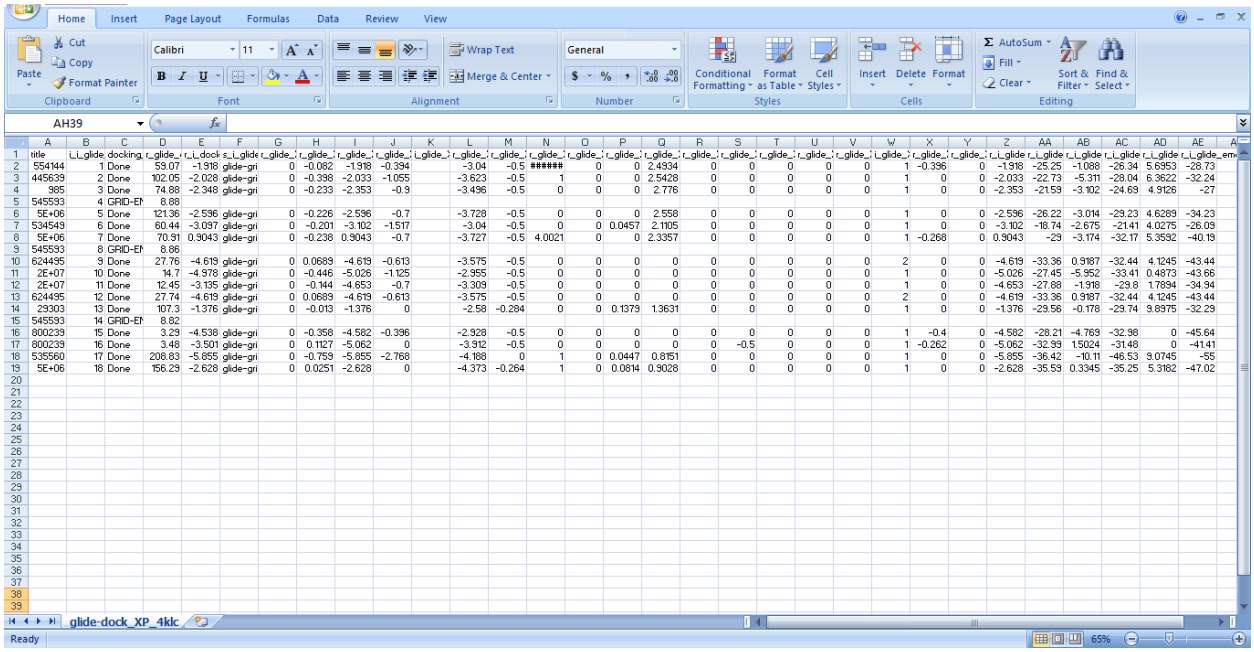
S.NO	RT (Min)	NAME OF THE COMPOUND
1	6.936	Udencanoic acid, 10-methyl-, methyl ester
2	9.037	Oleic acid
3	9.304	n-Hexadecanoic acid
4	9.756	Heptacosane, 1-chloro
5	10.358	2-Methyl-Z,Z-3,13-octadecadienol
6	10.675	Cyclopentaneundecanoic acid
7	12.620	7-Methyl-Z-tetradecen-ol acetate
8	12.877	Heptacosane,1-chloro-
9	13.272	3,4-Dihydrosioqinoline,1-[1-phenethyl]-6,7-dimethoxy-
10	13.694	4H-Dibenzo[de,g]quinoline,5,6,6a,7-tetrahydro-10,11-dimethoxy
11	13.932	3,4-Dihydrosioqinoline,1-[1-phenethyl]-6,7-dimethoxy-
12	14.125	1-Hexacosene

13	14.477	Heptacosane,1-chloro-
14	16.008	(+)-Roemerine
15	16.288	Spiro[2,5-cyclohexadiene-1,7'(1'H)-cyclopent[ij]isoquinolin]-4-
16	17.713	(-)-1,2,3,4-Tetrahydroisoquinolin-6-ol-l-carboxylic acid, 7-met
17	17.994	1,2,3,4-Tetrahydroisoquinolin-1-[phenyl(hydroxymethyl)]-6,7-d
18	18.645	(-)-1,2,3,4-Tetrahydroisoquinolin-6-ol-l-carboxylic acid, 7-met
19	19.083	2-Myristynoyl pantethenine
20	19.465	10-Heneicosene(c,t)

Schrödinger is a complete software package for drug discovery, including: induced fit and flexible docking mode based on receptor and ligand structure; docking mode based on receptor structure and ligand polarity; based on receptor structure and solution environment properties Docking mode of combinatorial chemical library; combinatorial chemical library design and docking mode based on combinatorial library; drug design based on ligand structure, pharmacophore and 3D-QSAR; biomolecular structure simulation, protein, sugar, nucleic acid, small peptide, etc.; based on target Drug design; ADME properties prediction. One important tool in the Schrödinger suite is Maestro. It can be downloaded as part as an Academic Campaign (http://www.schrodinger.com/freemaestro/) and is also useful for post-processing

All the selected 5 ligands showed good docking scores reflecting drug-binding affinities with 4KLC. All the selected ligands showed favorable molecular properties by satisfying Lipinski's rule of 5 and ADME profile. Five compounds out of the 20 screened compounds, showed

significant bioactivity scores as ion channel modulators: 2-Myristynoyl Pantethenine, (+)-Roemerine , 4H-Dibenzo[de,G]Quinoline,5,6,6A,7-Tetrahydro-10,11-Dimethoxy , 4HDibenzo[DE,G]Quinoline,5,6,6A,7-Tetrahydro-10,11-Dimethoxy and 3,4-Dihydrosioqinoline,1-[1-Phenethyl]-6,7- Dimethoxy. We speculate that the activity of 2-Myristynoyl Pantethenine against Cardio vascular disease could be due to inhibition by binding to 4KLC from our current in silico study.



title	i_i_glide_	docking_	r_glide_	r_i_dock	s_i_glide	r_glide_	r_glide_	r_glide_	r_glide_	i_glide_	r_glide_	r_glide_	r_glide_	r_glide_	r_glide_	r_glide_	r_glide_	r_glide_	r_glide_	r_glide_	i_glide_	r_glide_	r_glide_	r_i_glide	r_i_glide	r_i_glide	r_i_glide	r_i_glide	r_i_glide_em
554144	1	Done	53.07	-1.918	glide-gri	0	-0.082	-1.918	-0.334		-3.04	-0.5	######	0	0	2.4934	0	0	0	0	0	1	-0.396	0	-1.918	-25.25	-1.088	-26.34	5.6953	-28.73
445639	2	Done	102.05	-2.028	glide-gri	0	-0.398	-2.033	-1.055		-3.623	-0.5	1	0	0	2.5428	0	0	0	0	0	1	0	0	-2.033	-22.73	-5.311	-28.04	6.3622	-32.24
985	3	Done	74.88	-2.348	glide-gri	0	-0.233	-2.353	-0.9		-3.496	-0.5	0	0	0	2.776	0	0	0	0	0	1	0	0	-2.353	-21.59	-3.102	-24.69	4.9126	-27
545533	4	GRID-EN	8.88																										
5E+06	5	Done	121.36	-2.596	glide-gri	0	-0.226	-2.596	-0.7		-3.728	-0.5	0	0	0	2.558	0	0	0	0	0	1	0	0	-2.596	-26.22	-3.014	-29.23	4.6289	-34.23
534549	6	Done	60.44	-3.097	glide-gri	0	-0.201	-3.102	-1.517		-3.04	-0.5	0	0	0.0457	2.1105	0	0	0	0	0	1	0	0	-3.102	-18.74	-2.675	-21.41	4.0275	-26.09
5E+06	7	Done	70.91	0.9043	glide-gri	0	-0.238	0.9043	-0.7		-3.727	-0.5	4.0021	0	0	2.3357	0	0	0	0	0	1	-0.268	0	0.9043	-29	-3.174	-32.17	5.3592	-40.19
545533	8	GRID-EN	8.86																										
624495	9	Done	27.76	-4.619	glide-gri	0	0.0689	-4.619	-0.613		-3.575	-0.5	0	0	0	0	0	0	0	0	0	2	0	0	-4.619	-33.36	0.9187	-32.44	4.1245	-43.44
2E+07	10	Done	14.7	-4.978	glide-gri	0	-0.446	-5.026	-1.125		-2.955	-0.5	0	0	0	0	0	0	0	0	0	1	0	0	-5.026	-27.45	-5.952	-33.41	0.4873	-43.66
2E+07	11	Done	12.45	-3.135	glide-gri	0	-0.144	-4.653	-0.7		-3.309	-0.5	0	0	0	0	0	0	0	0	0	1	0	0	-4.653	-27.88	-1.918	-29.8	1.7894	-34.94
624495	12	Done	27.74	-4.619	glide-gri	0	0.0689	-4.619	-0.613		-3.575	-0.5	0	0	0	0	0	0	0	0	0	2	0	0	-4.619	-33.36	0.9187	-32.44	4.1245	-43.44
29303	13	Done	107.3	-1.376	glide-gri	0	-0.013	-1.376	0		-2.58	-0.284	0	0	0.1379	1.3631	0	0	0	0	0	1	0	0	-1.376	-29.56	-0.178	-29.74	9.8975	-32.29
545533	14	GRID-EN	8.82																										
800239	15	Done	3.29	-4.536	glide-gri	0	-0.358	-4.582	-0.396		-2.928	-0.5	0	0	0	0	0	0	0	0	0	1	-0.4	0	-4.582	-28.21	-4.769	-32.98	0	-45.64
800239	16	Done	3.48	-3.501	glide-gri	0	0.1127	-5.062	0		-3.912	-0.5	0	0	0	0	0	-0.5	0	0	0	1	-0.262	0	-5.062	-32.99	1.5024	-31.48	0	-41.41
535560	17	Done	208.83	-5.855	glide-gri	0	-0.759	-5.855	-2.768		-4.188	0	1	0	0.0447	0.8151	0	0	0	0	0	1	0	0	-5.855	-36.42	-10.11	-46.53	9.0745	-55
5E+06	18	Done	156.29	-2.628	glide-gri	0	0.0251	-2.628	0		-4.373	-0.264	1	0	0.0814	0.9028	0	0	0	0	0	1	0	0	-2.628	-35.59	0.3345	-35.25	5.3182	-47.02

Fig 02 : The glide dock results of docking in .csv format

	docking_st	r_glide_cp	r_i_dockin	s_i_glide_g	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	i_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	i_glide_XP
2	Done	208.83	-5.85465	glide-grid_	0	-0.75858	-5.85465	-2.76786		-4.18806	0	1.00003	0	0.044698	0.815111	0	0	0	0	0	1
3	Done	3.48	-3.50109	glide-grid_	0	0.112676	-5.06209	0		-3.91237	-0.5	0	0	0	0	0	-0.5	0	0	0	1
4	Done	14.7	-4.97805	glide-grid_	0	-0.44641	-5.02565	-1.12461		-2.95464	-0.5	0	0	0	0	0	0	0	0	0	1
5	Done	12.45	-3.13541	glide-grid_	0	-0.14386	-4.65261	-0.7		-3.30875	-0.5	0	0	0	0	0	0	0	0	0	1
6	Done	27.76	-4.61874	glide-grid_	0	0.068902	-4.61874	-0.61272		-3.57492	-0.5	0	0	0	0	0	0	0	0	0	2
7	Done	27.74	-4.61874	glide-grid_	0	0.068902	-4.61874	-0.61272		-3.57492	-0.5	0	0	0	0	0	0	0	0	0	2
8	Done	3.29	-4.53788	glide-grid_	0	-0.35766	-4.58198	-0.39635		-2.92797	-0.5	0	0	0	0	0	0	0	0	0	1
9	Done	60.44	-3.09667	glide-grid_	0	-0.20061	-3.10157	-1.51714		-3.04004	-0.5	0	0	0.045703	2.11051	0	0	0	0	0	1
10	Done	156.29	-2.62801	glide-grid_	0	0.02509	-2.62801	0		-4.3729	-0.26449	1	0	0.08145	0.902838	0	0	0	0	0	1
11	Done	121.36	-2.59562	glide-grid_	0	-0.22606	-2.59562	-0.7		-3.72759	-0.5	0	0	0	2.55803	0	0	0	0	0	1
12	Done	74.88	-2.34794	glide-grid_	0	-0.23263	-2.35284	-0.9		-3.49618	-0.5	0	0	0	2.77597	0	0	0	0	0	1
13	Done	102.05	-2.02833	glide-grid_	0	-0.39835	-2.03323	-1.05488		-3.62281	-0.5	1	0	0	2.54281	0	0	0	0	0	1
14	Done	59.07	-1.91814	glide-grid_	0	-0.08158	-1.91814	-0.39395		-3.03956	-0.5	3.24E-10	0	0	2.4934	0	0	0	0	0	1
15	Done	107.3	-1.37649	glide-grid_	0	-0.01336	-1.37649	0		-2.57976	-0.28436	0	0	0.137916	1.36308	0	0	0	0	0	1
16	Done	70.91	0.90432	glide-grid_	0	-0.23805	0.90432	-0.7		-3.72719	-0.5	4.00208	0	0	2.33568	0	0	0	0	0	1
17	GRID-ENEI	8.88																			
18	GRID-ENEI	8.86																			
19	GRID-ENEI	8.82																			

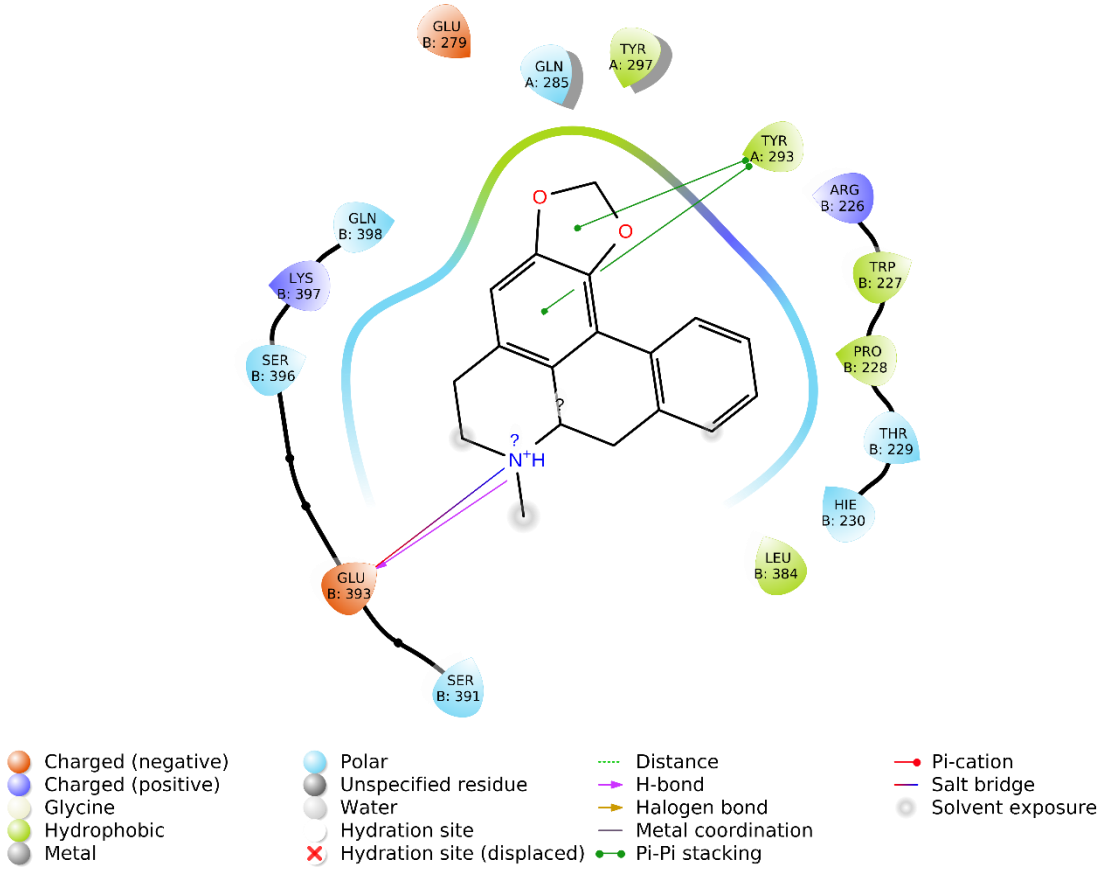
Fig 03 : zoomed glide dock results of docking in .csv format - 1

	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	r_glide_XP	i_glide_XP	r_glide_XP	r_glide_XP	r_i_glide_g	r_i_glide_g	r_i_glide_g	r_i_glide_g	r_i_glide_g	r_i_glide_emodel
2	-4.18806	0	1.00003	0	0.044698	0.815111	0	0	0	0	0	1	0	0	-5.85465	-36.4193	-10.1144	-46.5337	9.07449	-55.0008
3	-3.91237	-0.5	0	0	0	0	0	-0.5	0	0	0	1	-0.2624	0	-5.06209	-32.9865	1.50235	-31.4841	0	-41.4074
4	-2.95464	-0.5	0	0	0	0	0	0	0	0	0	1	0	0	-5.02565	-27.4548	-5.95208	-33.4069	0.487288	-43.6634
5	-3.30875	-0.5	0	0	0	0	0	0	0	0	0	1	0	0	-4.65261	-27.8827	-1.91812	-29.8008	1.78936	-34.9379
6	-3.57492	-0.5	0	0	0	0	0	0	0	0	0	2	0	0	-4.61874	-33.3604	0.918687	-32.4417	4.12452	-43.4363
7	-3.57492	-0.5	0	0	0	0	0	0	0	0	0	2	0	0	-4.61874	-33.3604	0.918687	-32.4417	4.12452	-43.4363
8	-2.92797	-0.5	0	0	0	0	0	0	0	0	0	1	-0.4	0	-4.58198	-28.2125	-4.76877	-32.9812	0	-45.6424
9	-3.04004	-0.5	0	0	0.045703	2.11051	0	0	0	0	0	1	0	0	-3.10157	-18.736	-2.67481	-21.4108	4.02749	-26.0894
10	-4.3729	-0.26449	1	0	0.08145	0.902838	0	0	0	0	0	1	0	0	-2.62801	-35.5859	0.334534	-35.2514	5.31819	-47.0184
11	-3.72759	-0.5	0	0	0	2.55803	0	0	0	0	0	1	0	0	-2.59562	-26.2165	-3.01412	-29.2306	4.62888	-34.2321
12	-3.49618	-0.5	0	0	0	2.77597	0	0	0	0	0	1	0	0	-2.35284	-21.5902	-3.10179	-24.692	4.91263	-26.9978
13	-3.62281	-0.5	1	0	0	2.54281	0	0	0	0	0	1	0	0	-2.03323	-22.7315	-5.3113	-28.0428	6.36221	-32.2398
14	-3.03956	-0.5	3.24E-10	0	0	2.4934	0	0	0	0	0	1	-0.39645	0	-1.91814	-25.2532	-1.08769	-26.3409	5.69532	-28.7319
15	-2.57976	-0.28436	0	0	0.137916	1.36308	0	0	0	0	0	1	0	0	-1.37649	-29.5625	-0.17813	-29.7406	9.89745	-32.2886
16	-3.72719	-0.5	4.00208	0	0	2.33568	0	0	0	0	0	1	-0.2682	0	0.90432	-28.9968	-3.17396	-32.1708	5.35916	-40.1885

Fig 04 : zoomed glide dock results of docking in .csv format - 2

2-MYRISTYNOYL PANTETHENINE

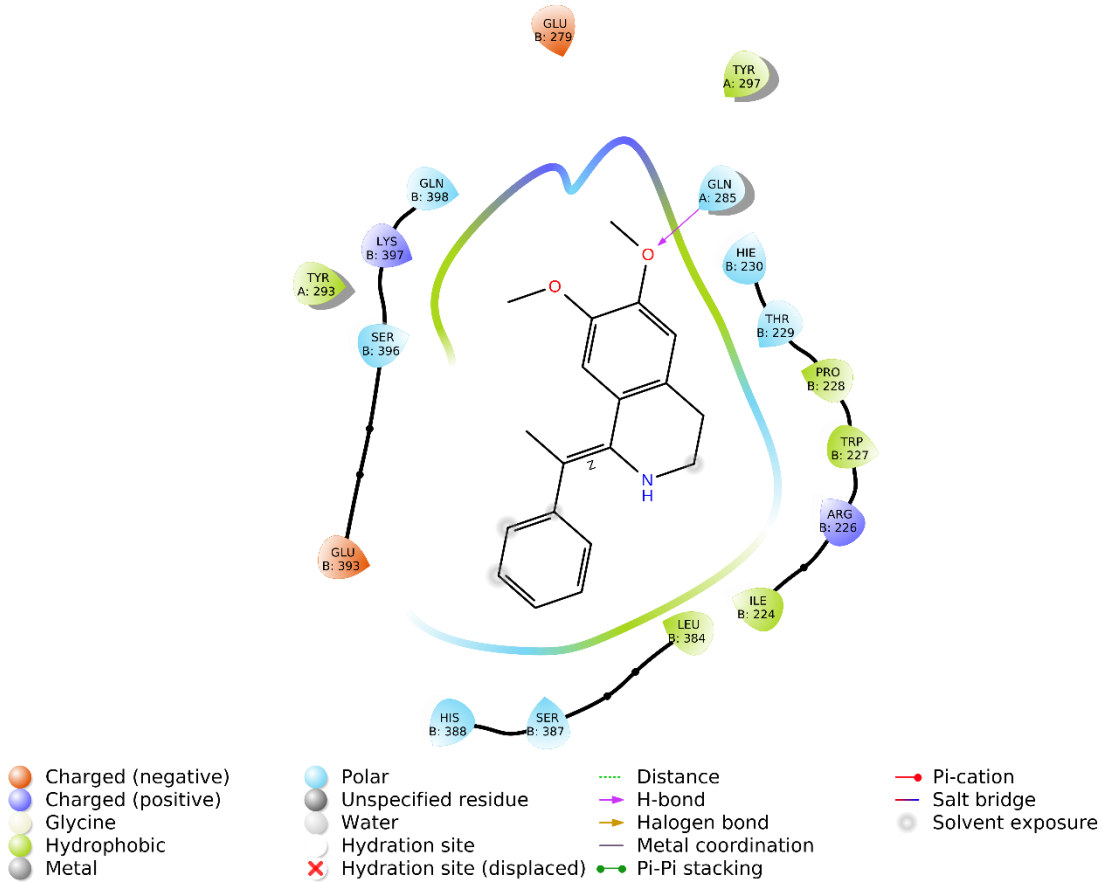
C25H44N2O5S



2-Myristynoyl Pantethenine (C25H44N2O5S) has the least glide dock score of -**5.85465**comparatively of all the compounds, which will be more interactive and effective. This compound will be bind with the receptor ie., protein at the target site easily

(+)-ROEMERINE

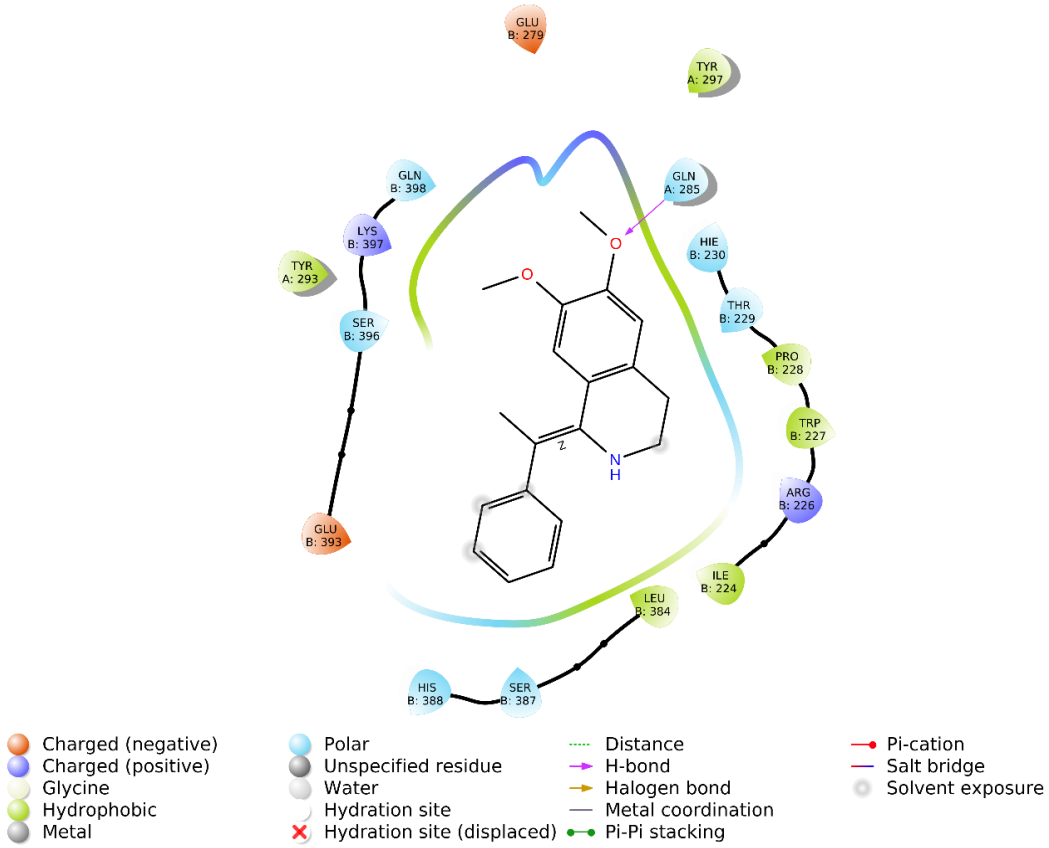
C18H17NO2



(+)-Roemerine (C18H17NO2) is the has second least glide dock score of -**5.06209** which is slightly less effective than the previous compound but it has the markable score so that it will also bind with our protein at the target site.

4H-DIBENZO[DE,G]QUINOLINE,5,6,6A,7-TETRAHYDRO-10,11-DIMETHOXY

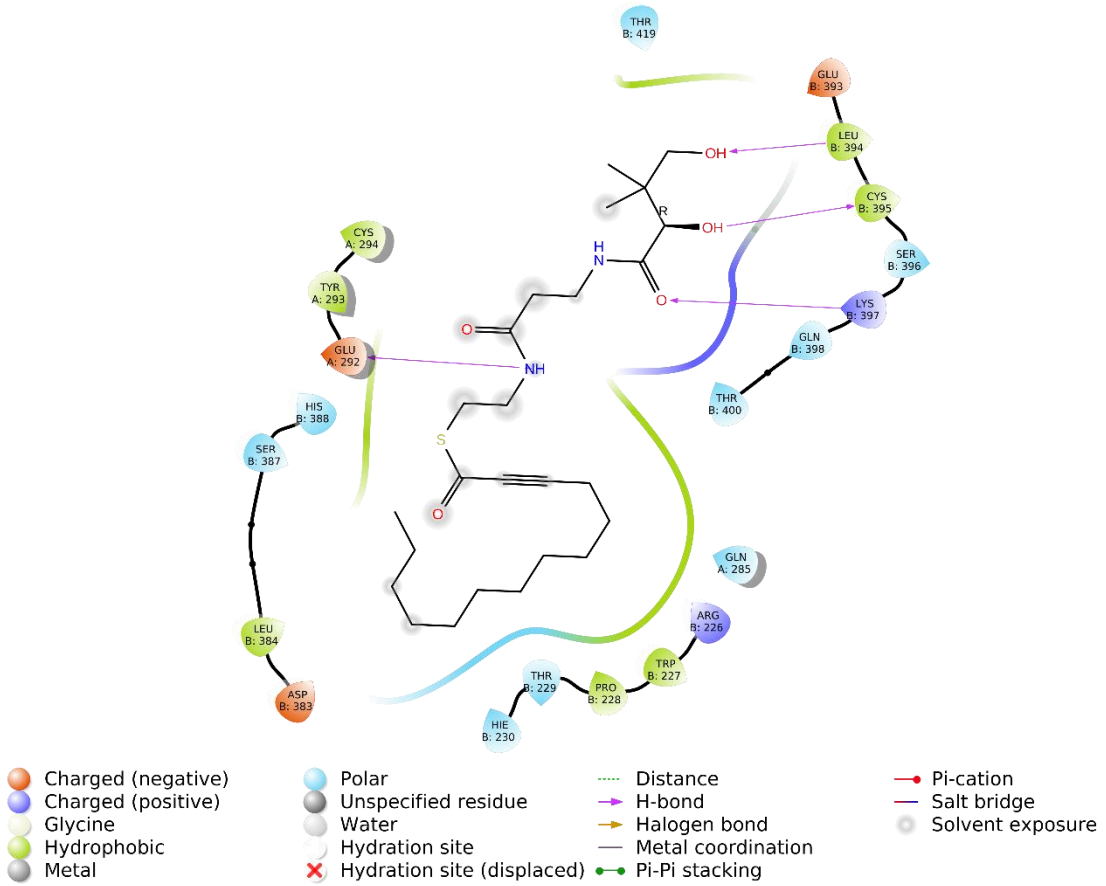
C19H21NO2



4H-Dibenzo[de,g]quinoline,5,6,6a,7-tetrahydro-10,11-dimethoxy (C19H21NO2) has got the third least glide dock score of **-5.02565**which is also an effective compound, to react with the target protein.

4H-DIBENZO[DE,G]QUINOLINE,5,6,6A,7-TETRAHYDRO-10,11-DIMETHOXY

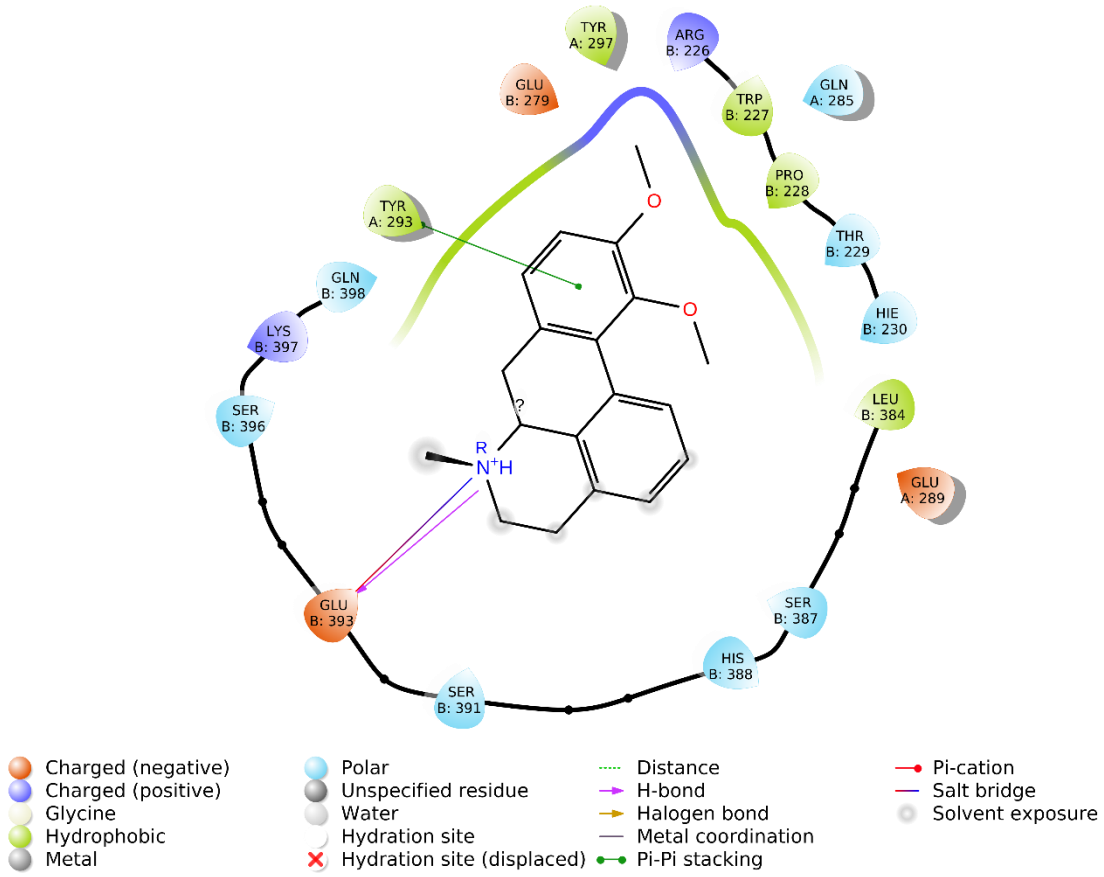
C19H21NO2



4H-Dibenzo[de,g]quinoline,5,6,6a,7-tetrahydro-10,11-dimethoxy (C19H21NO2) has got the fourth least glide dock score of **-4.65261**which is also an effective compound, to react with the target protein.

3,4-DIHYDROSIOQINOLINE,1-[1-PHENETHYL]-6,7-DIMETHOXY

C19H21NO



3,4-Dihydrosioqinoline,1-[1-phenethyl]-6, dimethoxy- (C19H21NO2) has got the fifth least glide dock score of **-4.61874** which is also intends to binds with our receptor protein.

CONCLUSION

CONCLUSION

All the selected 5 ligands showed good docking scores reflecting drug-binding affinities with 4KLC. All the selected ligands showed favourable molecular properties by satisfying Lipinski's rule of 5 and ADME profile. Five compounds out of the 20 screened compounds, showed significant bioactivity scores as ion channel modulators: 2-Myristynoyl Pantethenine, (+)-Roemerine, 4HDibenzo [de, G] Quioline,5,6,6A,7-Tetrahydro-10, 11-Dimethoxy, 4HDibenzo[DE, g] Quinoline,5,6,6A,7-Tetrahydro-10,11-Dimethoxy and 3,4-Dihydrosioqinoline, 1-[1-Phenethyl]-6,7-Dimethoxy. We speculate that the activity of 2-Myristynol Pantethenine against Cardio vascular disease could be due to inhibition by binding to 4KLC from our current in silico study. Futher this study can be done in animals and can be reported

REFERENCE

REFERENCE

Alakhova DY, Kabanov AV, *Mol Pharm.* 2014;11:2566.

Atsuko Itoh, Tomomi Saitoh, Kaori Tani, Misaki Uchigaki, Yumi Sugimoto, Jun Yamada, Hiroshi Nakajima, Hideo Ohshiro, Schujian Sun, Takao Tanahashi)

Bailey T.L., Boden M., Buske F.A., Frith M., Grant C.E., Clementi L., Ren J., Li W.W., Noble W.S. MEME SUITE: Tools for motif discovery and searching. *Nucleic Acids Res.* 2009;**37**:W202–W208. doi: 10.1093/nar/gkp335.

Bhoite R, Chandrasekaran A, Pratti VL, Satyavrat V, Aacharya S, Mane A, Mehta S, Kale RM, Nagamuthu G, Selvaraj S, Rajagopal G, Vasudevan S, Shanmugam S, Mohan AR, Unnikrishnan R, Krishnaswamy K, Mohan V.J Nutr Metab. 2021 Apr 15;2021:6634225. doi: 10.1155/2021/6634225. eCollection 2021.PMID: 33953977

Bogoyevitch M.A., Andersson M.B., Gillespie-Brown J., Clerk A., Glennon P.E., Fuller S.J., Sugden P.H. Adrenergic receptor stimulation of the mitogen-activated protein kinase cascade and cardiac hypertrophy. *Biochem. J.* 1996;314:115–121. doi: 10.1042/bj3140115.

Brand E., Chatelain N., Paillard F., Tiret L., Visvikis S., Lathrop M., Soubrier F., Demenais F. Detection of putative functional angiotensinogen (AGT) gene variants controlling plasma AGT levels by combined segregation-linkage analysis. *Eur. J. Hum. Genet.* 2002;**10**:715. doi: 10.1038/sj.ejhg.5200874.

Camejo-Rodrigues, J., Ascensao, L., Bonet, M. À. & NValles, J. An ethnobotanical study of medicinal and aromatic plants in the Natural Park of Serra de São Mamed" (Portugal). *J. Ethnopharmacol.* **89**(2–3), 199–209 (2003).

Campbell N.R., Lackland D.T., Lisheng L., Niebylski M.L., Nilsson P.M., Zhang X.H. Using the Global Burden of Disease study to assist development of nation-specific fact

sheets to promote prevention and control of hypertension and reduction in dietary salt: A resource from the World Hypertension League. *J. Clin. Hypertens.* 2015;**17**:165–167. doi: 10.1111/jch.12479. [

Cao, F. R., Xiao, B. X., Wang, L. S., Tao, X., Yan, M. Z., Pan, R. L., et al. (2017). Plasma and brain pharmacokinetics of ganoderic acid A in rats determined by a developed UFLC-MS/MS method. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 1052, 19–26. doi: 10.1016/j.jchromb.2017.03.009

Catalá López F., Tabarés Seisdedos R. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;**8**:1459–1544.

Cohn J.N., Ferrari R., Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J. Am. Coll Cardiol.* 2000;35:569–582. doi: 10.1016/S0735-1097(99)00630-0.

Drazner, M.H.; Rame, J.E.; Marino, E.K.; Gottdiener, J.S.; Kitzman, D.W.; Gardin, J.M.; Manolio, T.A.; Dries, D.L.; Siscovick, D.S. Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. *J. Am. Coll Cardiol.* **2004**, *43*, 2207–2215.
First published: 16 May 2021 **https://doi.org/10.1002/bab.2194).**

Ghazali, Siti Nur Akmal and Alias, Norsyuhada and Abdul Hamid *nelumbo nucifera*, AzzmerAzzar (2017) *Molecular docking of selected flavonoid compounds from as potential pancreatic lipase inhibitor.* In: 8th Malaysian Symposium of Biomedical Science, 12th-14th May 2017, Kuantan, Pahang. (Unpublished))
Gottesman MM, *Annu Rev Med.* 2002;53:615.

Jian Liu,YangLu,GuancongLi,MinXiao,Guangming Yang &Yang Pan. PagAes 379-394 | Received 27 Nov 2019, Accepted 23 Dec 2019, Accepted creator rendition posted on the web: 09 Jan 2020, Published on the web: 25 Jan 2020.

Jingfang Li, Ze-yuan Deng, Yushan He, Yawei Fan, Huanhuan Dong, Ronghua Chen, Ronghua Liu, Rong Tsao, Xiaoru Liu).

Journal of agricultural and food chemistry (2014-10-21)Yuan-Ting Zhu, Yan-Wei Jia, Yi-Ming Liu, Jian Liang, Li-Sheng Ding, Xun Liao)
LWT - Food Science and Technology (IF4.952), **Pub Date : 2021-05-15**, *DOI: 10.1016/j.lwt.2021.111728*

Mendis S., Puska P., Norrving B., World Health Organization . *Global Atlas on Cardiovascular Disease Prevention and Control*. World Health Organization; Geneva, Switzerland: 2011.

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee . Heart disease and stroke statistics—2015 update: a report from the American Heart Association. **Circulation**. 2015; 131:e29–e322. Rajendran HarishKumar,Chinnadurai Immanuel Selvaraj

Rohs R, Bloch I, Sklenar H, Shakked Z (2005) Molecular flexibility in ab-initio drug docking to DNA: binding-site and binding-mode transitions in all-atom Monte Carlo simulations. Nucl Acids Res 33: 7048-7057.

Subashini R, Sumathi P. Cardioprotective effect of *Nelumbo nucifera* on mitochondrial lipid peroxides, enzymes and electrolytes against isoproterenol induced cardiotoxicity in Wistar rats. Asian Pacific Journal of Tropical Disease 2;2012:588-91.

Tikekar, R. V., Ludescher, R. D. & Karwe, M. V. Processing stability of squalene in amaranth and antioxidant potential of amaranth extract. *J. Agric. Food Chem.* **56**, 10675–10678 (2008).

Westover D, Li F, *J Exp Clin Cancer Res.* 2015;34:159.

Wetzler M, et al. *Clin Lymphoma Myeloma Leuk.* 2013;13:430.