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Protein Ligand Docking Study of Cetirizine on HERG Receptor

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Abstract— HERG is the protein which is found in the potassium ion channel which is mainly used to check the cardiac action of heart in which we can see the heart rhythm and its abnormality by the Q.T syndrome through electro gram where Q.T interval was extended or prolonged for that the various reports are coming for sudden death due to cardiac arrest.

Keywords—Liagand, Potassium Membrane,Gene,HERG .

I. INTRODUCTION

During many years it has been found that various drugs wore withdrawn from the market as there are various reports of sudden death due to cardiac arrest.

In many of the above case the abnormality of the cardiac muscles repolarization was absorbed this can be characterized in the electro gram where the QT interval was extended or prolonged.

This abnormality induced ventricular tachycardia which caused degeneration and ventricular fibrillation resulting in sudden death.

It was noted that almost all cases in which cardiac action potential was prolonged was due to explosion of drug to block one specific mechanism found in the heart which was blocking of IKR current in the heart.

In various cases it was that the potassium ion channel which is encoded by HERG gene.

This HERG gene is mainly responsible and the rout caused of QT prolongation in electrocardiogram which is induced by drugs. This channels is the most crucial step for the repolarization of cardiac membrane.

HERG from the largest portion of the ion channels protein which is responsible for the conduction potassium ion in the muscles cell of the heart. If the dose of the drugs or its concentration is found to have affinity to word HERG ligand. Then this rises in affinity can caused in increased in the prolonged in QT interval.[1,2]

The FDA has been working from 2005 on this issue so that new molecular moieties are evaluated from TQT studies to find out the effect of drug.

HERG is the major form of ion channel protein which carries out potassium ion from the heart muscles. This HERG potassium channels are made up of 4alpha sub units and these subunit are forming channel like structure in plasma membrane.

These subunits are made up of 6 trance membrane helical like structure which as S1, S2, S3, S4, S5, S6 the S4 helix is made up of arranging and lysine in amino acid receptor. These allowed the channels by reacting to the voltage gradient by changing conformations and thus acting between conducting and non-conducting forms.[3,4]

This process is known as gating. These channels are very much sensitive to bind with the drug in the presence of decreased extracellular potassium, Membrane this can result in decreased channels functions.[5]

Cetirizine is the 2nd generation antihistamine drugs used to treat allergies chemical formula C21H25CIN2O3 it has also so many types adverse effect for example cardiac failure, tachycardia, fatigue etc.[6,7]

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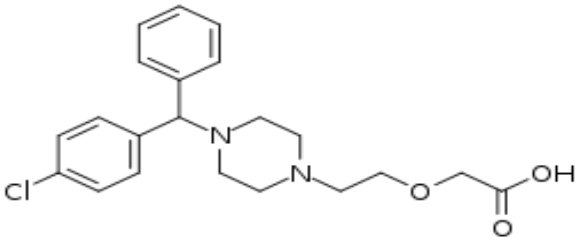

Fig -1.1Chemical Structure of CetirizineC21H25CIN2O3.

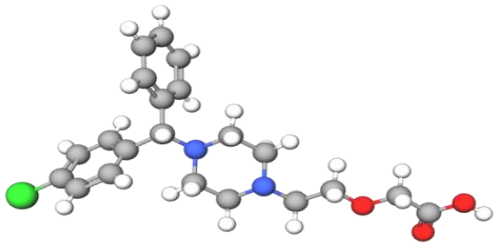

Fig -1.2 3D Structure of Cetirizine.

II. METHODOLOGY

For the purpose of molecular docking, structure of HERG solved at 1.46,A resolution was utilization . ligand docking was accomplished by the GOLD 4.0.1 (Genetic Optimization for Ligand Docking) program developed in CCDC (Cambridge Crystallographic Data Centre), UK.GOLD uses genetic algorithm for docking flexible ligand into the protein binding sites.

Thus, it uses the full range of ligand conformational flexibility with the protein binding sites residues, in which only side chains are made flexible during the docking process.[8]

Software are used then ligand HERG receptor are downloaded in PDB(Protein Data Bank)after that drug are docking in the GOLD software for molecule interaction. and we got hydrogen bond ,pi-pi interaction ,hydrophobic bond for that potassium channels inhibit, QT interval prolonged because of that cardiac arrest occurs.[9]

III. RESULTS AND DISCUSSION

The GOLD fitness score (GFS) was used to indicated the protein-ligand binding affinity.

Firstly we have drawn a drug structure in CAM 2D ULTRA after that CAM 3D ULTRA are used for energy minimization for minimization Gamess

The docking of cetirizine was performed in the cryo structure of HERG.GOLD 4.0.1 software was used for the docking process the binding radius was made 20 Armstrong and the geometric centre was selected as Y652 all the above binding was studies an a final lead was selected.

While examination the binding process which was obtained after docking it can be summarized that Cetirizine binding to the central cavity of the HERG channels and pi –pi bond and hydrogen bonding introduction with THR 623 (Subunit A) and TYR 652 (Subunit C). In the docking model it was observed the aromatic group of cetirizine was showing bonding with the size chain of (TYR652, Subunit C).

It was also noted that the hydrophobic group was showing bonding with the benzene ring of PHE-656 from the above studies we can concluded that cetirizine was inhibiting HERG channels and hence it was inhibiting the current which was flowing through these channels this caused extension of QT channels and thus prolonged the cardiac action potential.

The result obtained in the above studies through light on the side effect which is caused by consuming cetirizine in large dosage leading to cardiac failure

Fig- 2.3 Central cavity of the HERG channels where, pi –pi bond and hydrogen bonding introduction with THR 623 (Subunit A) and TYR 652 (Subunit C) where aromatic group of drug was showing bonding with the size chain of (TYR652, Subunit C). shown in the figure.

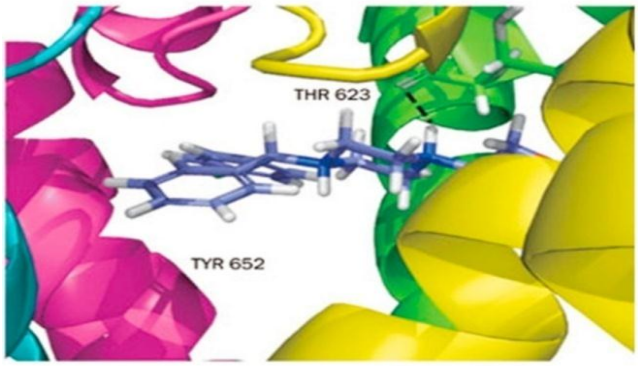

Fig-2.3

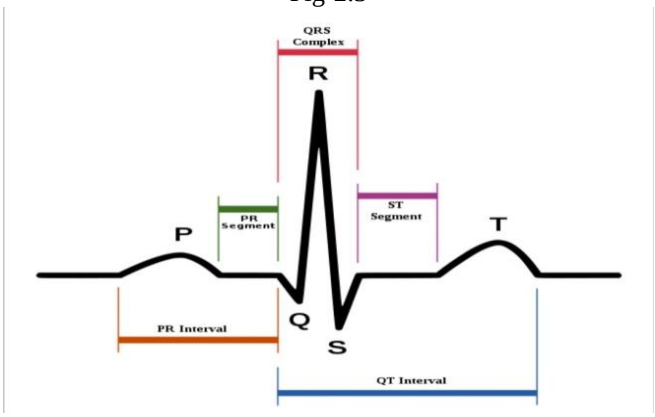

Fig-2.4 In the cardiac heart rates PQRST where the QT interval is prolonged due to the effect of drug as shown in the figure.

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REFERENCES

[1] Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. *Torsade de pointes Due to Noncardiac Drugs: Most Patients Have Easily Identifiable Risk* Factors. Medicine (Baltimore). **2003; 82:282–290.**

[2] Hancox JC, McPate MJ, El Harchi A, Zhang YH. *The HERG Potassium Channel and HERG Screening* For Drug-Induced Torsades de Pointes. Pharmacol Ther. **2008; 119:118–132**

[3] Lees-Miller, J. P., Duan, Y., Teng, G. Q. & Duff, H. J. Molecular *Determinant of High-Affinity Dofetilide Binding to HERG1 Expressed in Xenopus Oocytes: Involvement of S6 Sites*. Mol. Pharmacol**. 57**, **367–374** (2000).

[4] Curran MP, scott LJ, Perry CM. *Cetirizine: a Review of Its Use in Allergic Disorders. Drugs* 2004; **64: 523–61.**

[5] Mitcheson JS, Chen J, Sanguinetti MC. *Trapping of a Methane Sulfonanilide by Closure of the HERG Potassium Channel Activation Gate*. J Gen Physiol. 2000; **115:229–240**

[6] Sheiner L, Beal S. Nonmem, Version 5.1. *Nonmem Project Group. San Francisco:* University of California, 1998.

[7] Carmeliet,e.(1993). *Use-Dependent Block and Use-Dependent Unblock of the Delayed Rectifier k+ Current by Almokalant in Rabbit Ventricular Myocytes.* circ. Res.,**73**,**857–868**.

[8] Keating,m.t.&Sanguinetti,m.c.(2001).*Molecular and Cellular Mechanisms of Cardiac Arrhythmias*.Cell,**104**,**569–580.**

[9] Bucchi A, Baruscotti M, Nardini M, Barbuti A, Micheloni S, Bolognesi M, DiFrancesco D. *Identification of the Molecular Site of Ivabradine Binding to HCN4 Channels*. PLoS One**. 2013; 8:e53132**

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