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DRUG DESIGN: PHENOBOLA AS CLATHRIN MEIDATED ENDOCYTOSIS INHIBITOR AND EBOLA VIRUS TREATMENT

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ABSTRACT

Background: Ebola virus is a very serious contagious disease spread in Africa and other countries and it transmit by bats to human. Its symptoms range from fever to body organs bleeding.it outbreak started in many different places around the world. **Aim:** is to design a drug that block Clathrin mediated endocytosis (CME) cycle so as to prevent the virus from entering the body host cell. The virus uses the CME to enter and replicate. **Material and Method:** using ChemSketch to draw and determine the drug molecule, and using OpenBabel online server to transfer the molecule into MOL2 format so as to be apply in SwissDock server, then chose the target protein from protein database bank using PDB id of CME then insert in SwissDock and submit it to get the docking result. **Result:** a new drug that can prevent and bock the clathrin-mediated endocytosis (CME) cycle called Phenobola one of other CME blocker and inhibitor. And can treat Ebola virus by prevent entering into the host cell.

INTRODUCTION

also known as Ebola virus disease (EVD) or Ebola hemorrhagic fever (EHF), is a viral hemorrhagic fever of humans and other primates caused by Ebola viruses.(WHO, 2014)Signs and symptoms typically start between two days and three weeks after contracting the virus

with a fever, sore throat, muscular pain, and headaches.(WHO, 2014). Vomiting, diarrhea and rash usually follow, along with decreased function of the liver and kidneys.[1] At this time, some people begin to bleed both internally and externally.(WHO, 2014) The disease has a high risk of death, killing 25% to 90% of those infected, with an average of about 50%. (WHO, 2014) This is often due to low blood pressure from fluid loss, and typically follows six to 16 days after symptoms appear. (*Singh SK, et al , 2014).*

The virus spreads through direct contact with body fluids, such as blood from infected humans or other animals.(WHO,2014) Spread may also occur from contact with items recently contaminated with bodily fluids.(WHO,2014) Spread of the disease through the air between primates, including humans, has not been documented in either laboratory or natural conditions. Semen or breast milk of a person after recovery from EVD may carry the virus for several weeks to months.(WHO, 2014).Fruit bats are believed to be the normal carrier in nature, able to spread the virus without being affected by it.. Other diseases such as malaria, cholera, typhoid fever, meningitis and other viral hemorrhagic fevers may resemble EVD. Blood samples are tested for viral RNA, viral antibodies or for the virus itself to confirm the diagnosis.(WHO,2014).

Control of outbreaks requires coordinated medical services and community engagement. This includes rapid detection, contact tracing of those who have been exposed, quick access to laboratory services, care for those infected, and proper disposal of the dead through cremation or burial (WHO, 2014) Samples of body fluids and tissues from people with the disease should be handled with special caution. Prevention includes limiting the spread of disease from infected animals to humans by handling potentially infected bush meat only while wearing protective clothing, and by thoroughly cooking bush meat before eating it(WHO, 2014) It also includes wearing proper protective clothing and washing hands when around a person with the disease.(WHO, 2014) An Ebola vaccine was approved in the United States in December 2019.(FDA, 2019) While there is no approved treatment for Ebola as of 2019.(NIH, 2019)two treatments (REGN-EB3 and mAb114) are associated with improved outcomes. Supportive efforts also improve outcomes.(WHO, 2019) This includes either oral rehydration therapy (drinking slightly sweetened and salty water) or giving intravenous fluids as well as treating symptoms.(WHO, 2014). (Inmazeb) was approved for medical use in the United States in October 2020, for the treatment of infection caused by *Zaire Ebola virus*.(FDA, 2014).

The disease was first identified in 1976, in two simultaneous outbreaks: one in Nzara (a town in South Sudan) and the other in Yambuku (Democratic Republic of the Congo), a village relatively near the Ebola River from which the disease takes its name.EVD outbreaks occur intermittently in tropical regions of sub-Saharan Africa.(WHO, 2014). From 1976 to 2012, the World Health Organization reports 24 outbreaks involving 2,387 cases with 1,590 deaths. The largest outbreak to date was the epidemic in West Africa, which occurred from December 2013 to January 2016, with 28,646 cases and 11,323 deaths.(WHO, 2019). It was declared no longer an emergency on 29 March 2016.(WHO, 2016). Other outbreaks in Africa began in the Democratic Republic of the Congo in May 2017.(WHO, 2017) and 2018. In July 2019, the World Health Organization declared the Congo Ebola outbreak a world health emergency.

The length of time between exposure to the virus and the development of symptoms (incubation period) is between two and 21 days. (WHO, 2014) and usually between four and ten days. (*Haas CN, 2104).* However, recent estimates based on mathematical models predict that around 5% of cases may take greater than 21 days to develop. (*Haas CN, 2014).*

Symptoms usually begin with a sudden influenza-like stage characterized by feeling tired, fever, weakness, decreased appetite, muscular pain, joint pain, headache, and sore throat. (*Haas CN, 2014).* The fever is usually higher than 38.3 °C (101 °F.)(*Hoenen T,et al, 2006).* This is often followed by nausea, vomiting, diarrhea, abdominal pain, and sometimes hiccups.+3.0.3 The combination of severe vomiting and diarrhea often leads to severe dehydration. Next, shortness of breath and chest pain may occur, along with swelling, headaches, and confusion. (*Magill A (2013).* In about half of the cases, the skin may develop a maculopapular rash, a flat red area covered with small bumps, five to seven days after symptoms be.

In some cases, internal and external bleeding may occur.(WHO, 2014) This typically begins five to seven days after the first symptoms. All infected people show some decreased blood clotting. (.)(*Hoenen T,et al, 2006).* Bleeding from mucous membranes or from sites of needle punctures has been reported in 40–50% of cases. This may cause vomiting blood, coughing up of blood, or blood in stool. Bleeding into the skin may create petechiae, purpura, ecchymoses or hematomas (especially around needle injection sites).Bleeding into the whites of the eyes may also occur. Heavy bleeding is uncommon; if it occurs, it is usually in the gastrointestinal tract. The incidence of bleeding into the gastrointestinal tract was reported to

be ~58% in the 2001 outbreak in Gabon. but in the 2014-15 outbreak in the US it was ~18%, possibly due to improved prevention of disseminated intravascular coagulation. (*Shantha JG, et al, 2016).*

Recovery may begin between seven and 14 days after first symptoms. (*Magill A (2013).* Death, if it occurs, follows typically six to sixteen days from first symptoms and is often due to low blood pressure from fluid loss. (*Singh SK, et al, 2014).* In general, bleeding often indicates a worse outcome, and blood loss may result in death. (*Gatherer D (August 2014))* People are often in a coma near the end of life. (*Magill A (2013).*

Those who survive often have ongoing muscular and joint pain, liver inflammation, and decreased hearing, and may have continued tiredness, continued weakness, decreased appetite, and difficulty returning to pre-illness weight. (*Magill A (2013).* Problems with vision may develop. It is recommended that survivors of EVD wear condoms for at least twelve months after initial infection or until the semen of a male survivor tests negative for Ebola virus on two separate occasions. (SRHD, 2020).

Survivors develop antibodies against Ebola that last at least 10 years, but it is unclear whether they are immune to additional infections. (CDC, 2014).

EVD in humans is caused by four of five viruses of the genus *Ebolavirus*. The four are Bundibugyo virus (BDBV), Sudan virus (SUDV), Taï Forest virus (TAFV) and one simply called Ebola virus (EBOV, formerly Zaire Ebola virus) (.*Hoenen T, et al, 2012)* EBOV, species *Zaire ebolavirus*, is the most dangerous of the known EVD-causing viruses, and is responsible for the largest number of outbreaks. (*Kuhn JH, et al, 2010*The fifth virus, Reston virus (RESTV), is not thought to cause disease in humans, but has caused disease in other primates. (*Spickler, Anna,2015)* All five viruses are closely related to marburgviruses. ((.*Hoenen T, et al, 2012).*

Ebola viruses contain single-stranded, non-infectious RNA genomes. (*Chippaux JP,2014) Ebolavirus* genomes contain seven genes including 3'-UTR-*NP-VP35-VP40-GP-VP30-VP24-L*-5'-UTR.. The genomes of the five different Ebola viruses (BDBV, EBOV, RESTV, SUDV and TAFV) differ in sequence and the number and location of gene overlaps. As with all filoviruses, ebolavirus virions are filamentous particles that may appear in the shape of a

shepherd's crook, of a "U" or of a "6," and they may be coiled, toroid or branched. In general, ebolavirions are 80 nanometers (nm) in width and may be as long as 14,000 nm.

Their life cycle is thought to begin with a virion attaching to specific cell-surface receptors such as C-type lectins, DC-SIGN, or integrins, which is followed by fusion of the viral envelope with cellular membranes. (*Misasi J, Sullivan NJ,2014).* The virions taken up by the cell then travel to acidic endosomes and lysosomes where the viral envelope glycoprotein GP is cleaved. (*Misasi J, Sullivan NJ, 2014).*This processing appears to allow the virus to bind to cellular proteins enabling it to fuse with internal cellular membranes and release the viral nucleocapsid. (*Misasi J, Sullivan NJ, 2014).* The *Ebolavirus* structural glycoprotein (known as GP1,2) is responsible for the virus' ability to bind to and infect targeted cells. The viral RNA polymerase, encoded by the *L* gene, partially uncoats the nucleocapsid and transcribes the genes into positive-strand mRNAs, which are then translated into structural and nonstructural proteins. The most abundant protein produced is the nucleoprotein, whose concentration in the host cell determines when L switches from gene transcription to genome replication. Replication of the viral genome results in full-length, positive-strand antigenomes that are, in turn, transcribed into genome copies of negative-strand virus progeny. (*Kühl A, Pöhlmann S, 2014)* Newly synthesised structural proteins and genomes self-assemble and accumulate near the inside of the cell membrane. Virions bud off from the cell, gaining their envelopes from the cellular membrane from which they bud. The mature progeny particles then infect other cells to repeat the cycle. The genetics of the Ebola virus are difficult to study because of EBOV's virulent characteristics. (*Olejnik J, et al, 2011).*

It is believed that between people, Ebola disease spreads only by direct contact with the blood or other body fluids of a person who has developed symptoms of the disease. Body fluids that may contain Ebola viruses include saliva, mucus, vomit, feces, sweat, tears, breast milk, urine and semen. The WHO states that only people who are very sick are able to spread Ebola disease in saliva, and the virus has not been reported to be transmitted through sweat. Most people spread the virus through blood, feces and vomit. Entry points for the virus include the nose, mouth, eyes, open wounds, cuts and abrasions. Ebola may be spread through large droplets; however, this is believed to occur only when a person is very sick. (CDC, 2014). This contamination can happen if a person is splashed with droplets. (CDC,2014). Contact with surfaces or objects contaminated by the virus, particularly needles and syringes, may also transmit the infection.(CDC, 2014) The virus is able to survive on objects for a few

hours in a dried state, and can survive for a few days within body fluids outside of a person.(CDC, 2020).

The Ebola virus may be able to persist for more than three months in the semen after recovery, which could lead to infections via sexual intercourse. (CDC, 2015). Virus persistence in semen for over a year has been recorded in a national screening programme. Ebola may also occur in the breast milk of women after recovery, and it is not known when it is safe to breastfeed again. (CDC,2014). The virus was also found in the eye of one patient in 2014, two months after it was cleared from his blood. Otherwise, people who have recovered are not infectious. (*Chippaux JP, 2014).*

The potential for widespread infections in countries with medical systems capable of observing correct medical isolation procedures is considered low. Usually when someone has symptoms of the disease, they are unable to travel without assistance. (*Pringle, C, et al, 2005).*

Dead bodies remain infectious; thus, people handling human remains in practices such as traditional burial rituals or more modern processes such as embalming are at risk. 69% of the cases of Ebola infections in Guinea during the 2014 outbreak are believed to have been contracted via unprotected (or unsuitably protected) contact with infected corpses during certain Guinean burial rituals. (CDC, 2014).

Health-care workers treating people with Ebola are at greatest risk of infection. (CDC, 2014). The risk increases when they do not have appropriate protective clothing such as masks, gowns, gloves and eye protection; do not wear it properly; or handle contaminated clothing incorrectly. (CDC, 2014). This risk is particularly common in parts of Africa where the disease mostly occurs and health systems function poorly. (*Tiaji Salaam, ET AL, 2014).* There has been transmission in hospitals in some African countries that reuse hypodermic needles. Some health-care centres caring for people with the disease do not have running water. In the United States the spread to two medical workers treating infected patients prompted criticism of inadequate training and procedures. (CDC, 2014).

Human-to-human transmission of EBOV through the air has not been reported to occur during EVD outbreaks. (WHO, 2014). And airborne transmission has only been demonstrated in very strict laboratory conditions, and then only from pigs to primates, but not from

primates to primates. Spread of EBOV by water, or food other than bush-meat, has not been observed. No spread by mosquitos or other insects has been reported. Other possible methods of transmission are being studied (CDC, 2014).

The natural reservoir for Ebola has yet to be confirmed; however, bats are considered to be the most likely candidate. (*Chowell G, Nishiura H, 2014).* Three types of fruit bats (*Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata*) were found to possibly carry the virus without getting sick. As of 2013, whether other animals are involved in its spread is not known. Plants, arthropods, rodents, and birds have also been considered possible viral reservoirs.(WHO,2014)

Bats were known to roost in the cotton factory in which the first cases of the 1976 and 1979 outbreaks were observed, and they have also been implicated in Marburg virus infections in 1975 and 1980.(*Pourrut X, et al, 2005).* Of 24 plant and 19 vertebrate species experimentally inoculated with EBOV, only bats became infected. (*Swanepoel R,et al, 1996).* The bats displayed no clinical signs of disease, which is considered evidence that these bats are a reservoir species of EBOV. In a 2002–2003 survey of 1,030 animals including 679 bats from Gabon and the Republic of the Congo, immunoglobulin G (IgG) immune defense molecules indicative of Ebola infection were found in three bat species; at various periods of study, between 2.2 and 22.6% of bats were found to contain both RNA sequences and IgG molecules indicating Ebola infection. (*Leroy EM, et al, 2005).* Antibodies against Zaire and Reston viruses have been found in fruit bats in Bangladesh, suggesting that these bats are also potential hosts of the virus and that the filoviruses are present in Asia. (*Olival KJ, et al, 2013).*

Clathrin-mediated endocytosis is away by which Ebola-virus enters the host cell. This process is very similar to macropinocytosis in that the plasma membrane forms invaginations that engulf the cell. However, clathrin-mediated endocytosis is different in that proteins on the surface of the host's surface, and in particular clathrin, facilitate the attachment of the virus to the host's cell surface. Glycoproteins are still used to attach the virus to the cell surface, and the NP-C1 cholesterol transporter still facilitates the fusion of the virus with endosomes and lysosomes and still allows the virus to escape into the cytoplasm. Without the NPC1 cholesterol transporter, Ebola-virus cannot leave the vesicle in order to replicate and cause infection in other cells.

To penetrate the cell, the viral membrane fuses with vesicle membrane, and the nucleo-capsid is released into the cytoplasm.In some culture cells, GP glycoprotein can be processed by host Cathepsin L andCathepsin B into 19kDa GP1. But this processing is not happening in all cells or for all Ebola virus. 19kDA GP1 interacts with host NPC1, which is highly expressed in dendritic cells. Fusion of virus membrane with the vesicle membrane is triggered by either low pH or NPC1 binding. In this study will design a drug that can block or prevent the CME so as not allow the virus to enter the cell mainly to the clathrin protein.

Due to this importance of the disease in this study will design a drug using software tools to block or inhibit Clathrin-meidated endocytosis (CME) cycle which use by the virus and stop replication.

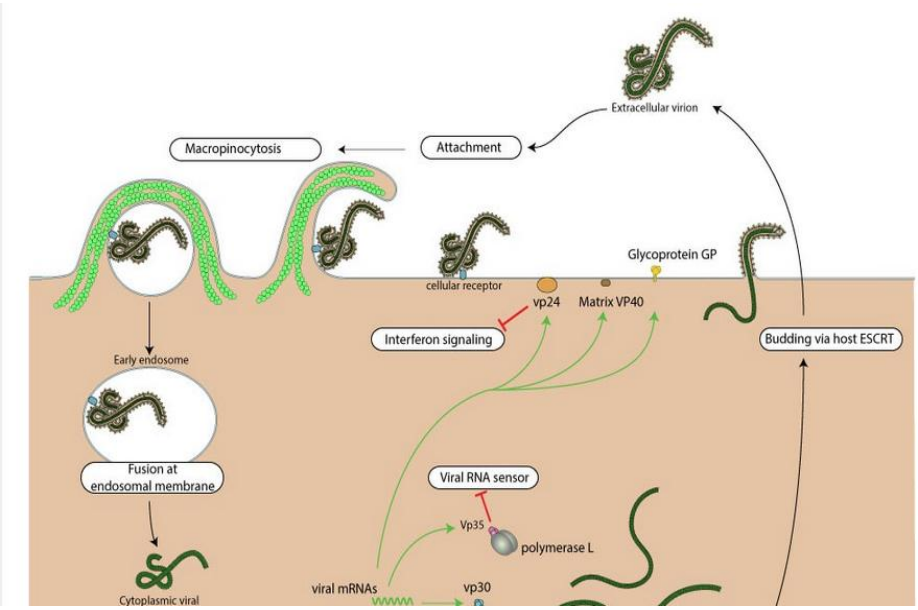

Figure 1: Show the Clathrin – mediated endocytosis cycle (CME)-(*WHO,2014*).

MATERIAL AND METHOD

ChemSketch/ACD lab: (https://www.acdlabs.com/resources/freeware/index.php). is a software that use to draw chemical structures and elements that use in chemistry and drugs. The website contains many software tools that can use in different chemical aspects, starting from drawing till applying the software in different from aspects.

OpenBabel GUI (https://sourceforge.net/projects/openbabel/) is a chemical toolbox designed to speak the many languages of chemical data. It's an open, collaborative project allowing anyone to search, convert, analyze or store data from molecular modeling chemistry, biochemistry or related areas.

Swiss Dock: (http://www.swissdock.ch/) is a web service to predict the molecular interactions that may occur between a target protein and a small molecule mainly a drug or chemical compounds.

RESULTS

Using the ChemSkecth to draw suitable chemical structure, which can block the CME cycle and prevent the virus from entering the host cell. The suitable predicted chemical drug is 5,10-dihydroacridophospine-phosphane(1/1) (phenobola). figure (1) show the structure of phenobole. After design and drawing the drug structure we change the mode of chemical appearance to mol2 reading file using OpenBabel so as to be read and apply using SwissDock server. Then insert the file into SwissDock, which dock the ligand and the target. The target is clathrin-meidtaed endocytosis protein with PDB ID (SVKY) and the ligand is our phenobola predicted drug. Figure (2) show the result of docking.

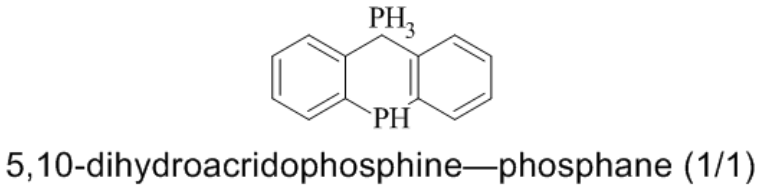

Figure 2: Structure of phenobola drug.

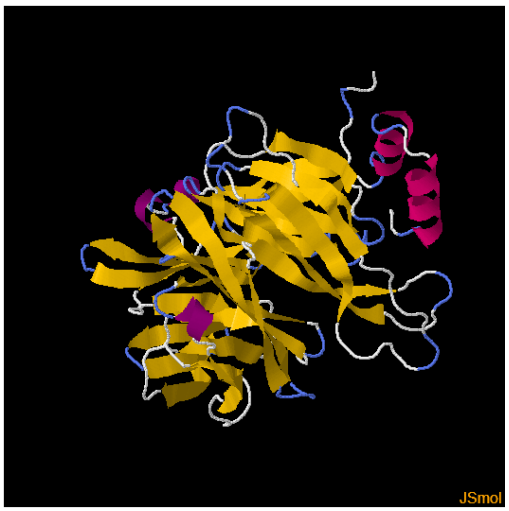

Figure 3: Result of docking.

In this study the pharmacological effect of Phenobola show that it's a water soluble in both classes with log s(ESOL) = -3.22 and solubility =1.30e-01 mg/ml ; 6.03e-04 mol/l and with

log s (Ali) = -2.44 and solubility 7.92e-01 mg/ml ; 3.66e-03 mol/l. in log s (SILCOS-IT) = -5.13 with solubility 1.58e-03 mg/ml ; 7.33e-06 mol/l.

Table 1: Show result of water solubility.

Water Solubility	
Log *S* (ESOL)	-3.22
Solubility	1.30e-01 mg/ml ; 6.03e-04 mol/l
Class	Soluble
Log *S* (Ali)	-2.44
Solubility	7.92e-01 mg/ml ; 3.66e-03 mol/l
Class	Soluble

Pharmacokinetics

Due to its solubility above the drug have high GI absorption mode and its also can pass the blood brain barrier BBB permeant. Predicting penetration into blood brain barrier means that the molecule is able to pass through this barrier is crucial in pharmaceutical sphere. Knowledge about interaction of molecules with cytochrome p450 (CYP)is also essential. This superfamily of isoenzymes participates in a fundamental way in the metabolism, biotransformation and elimination of drugs. Its estimated that 50 to 90% of therapeutic molecules can be substrates of the five major isoform (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4).Also it's not a P-gp substance which is a very importance in drug assimilation and metabolism. It inhibits CYP1A2, CYP2C19 and CYP3A4 enzymes but not inhibit the CYP2C9 and CYP2D6. Inhibition of these isoenzymes is one of the main causes of drug interactions, toxic effects or adverse effects due to less purification and accumulation of the drug or its metabolites in the body. With skin permeation logk = -6.04cm/s which can be deliver using water no other substances in the body. The prediction of permeability coefficient (Kp) for the absorption of molecules by the epidermis of mammals is based on the linear model built by potts and Guy, thus the more negative the log kp the less the molecule permeates. Phenobola is a p-glycoprotein inhibitor but not as substrate. This result fundamental to deduce about active efflux through biological membrane since p-glycoprotein constitute a class of efflux or secretion transporters that act as a barrier to absorption in numerous compartments such as in the gastrointestinal membranes and lumen wall or in the membranes of the brain. An important role of p-gp is to protect the CNS from xenobiotic and

if the molecule can act as an inhibitor, it reinforces the possibility of crossing the blood brain barrier.

Table (2): show result of pharmacokinetics.

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.04 cm/s

The lipiniske druglikness is record as 0 violation which can be a good drug to use also with good in Ghose, veber, Egan and Muegg. And these are evaluate drug-likeness in different parameters, Ghose evaluation by computing physiochemical property, presence of functional groups and important substructures, Eagn predict the drug absorption based on physical processes involved in membrane permeability Viber model characteristics molecules as drug-like if they have 10 or fewer rotatable bonds and a PSA (polar surface area), Muegg model is a database independent pharmacophore point filter that discriminate between drug like and nondrug like chemical matter ketone, hydroxyl, sulfonyl and amine groups are considered to be the most important four functional motifs in drug like molecules included in all mentioned drug like parameters.

Table 3: Show result of Druglikeness.

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

The phenobola with 0.55 bioavailability score which mean is a good permeable compound as a drug that is F < 10. The compounds don't give a false result in PAINS (Pan-assay interference compounds) which are chemical compounds that often gives false positive results in high throughout screens tend to react nonspecifically with numerous biological targets rather than specifically affecting one desired target.

The objective of Medicinal chemistry is to support the daily effort in drug discovery and help to find any problematic fragments in the molecule and phenobola drug have no such fragment.

Also the Brenck show 1 compound with alert that is phosphor but it's not a separate element its link with compound so it has no potentially problematic effect. The structural alert indicated by the Brenck is purely based on the knowledge of a compilation of chemical parts known to be toxic, metabolically unstable or with properties responsible for poor pharmacokinetics. The phenobola compound with lead-likeness follow a normal rules of drug discovery which uses nowadays by scientists and the chemists in industry but have a molecular weight of less than 250 (MW<250. With 3.69 synthetic bioavailability score it shows that phenobola is not a difficult drug to synthesize molecule. This value is a score based on the fragmented analysis of structures of more than 13 million compounds with hypothesis that the more a molecular fragment is frequent, the easier it is to obtain the molecule. The score is defined between 1 (easy synthetic) and 10 (very difficult synthesis.

Table 4: Show result of Medicinal chemistry.

	Medicinal Chemistry
PAINS	0 alert
Brenk	1 alert: phosphor
Leadlikeness	No; 1 violation: MW<250
Synthetic accessibility	3.69

The lipophilicity or liposolubility (LogP) is a property of great significance and is used as an indicator of the oral bioavailability of drug candidate molecules also constituting one of the main parameters of ADME/Tox. In general the optimization of the gastrointestinal absorption profile the rough passive diffusion after oral administration of a prototype candidate drug is achieved through the balance of its permeability and water solubility profile known as log P

or log D.phenobola showed presented average of 2,54 for log P. classified as optimal for good intestinal absorption due to the balance between water solubility and permeability rate by passive diffusion. Extreme values result in unbalance in these profiles with capacity to negatively impact the oral bioavailability profile. In addition the increase in lipophilicity values is involved in toxic properties such as blocking of CYP450 and hERG aswell as phospholipidosis induction. Thus there is relevant evidence suggesting that controlling lipophilicity among all the physiochemical properties within a defined ideal range improves the quality of a molecule and consequently the probability of therapeutic success.

Table 5: Show result of Lipophilicity.

	Lipophilicity
Log $P_{o/w}$ (iLOGP)	2.64
Log $P_{o/w}$ (XLOGP3)	2.23
Log $P_{o/w}$ (WLOGP)	1.26
Log $P_{o/w}$ (MLOGP)	3.48
Log $P_{o/w}$ (SILICOS-IT)	3.06
Consensus Log $P_{o/w}$	2.54

In this study predicted the physiochemical properties are important and necessary to understand and design new pharmacological compounds with the ability to bind to various biological targets and present beneficial effects to the body leading to the discovery of new treatments for diseases of more complex origin such as Ebola virus disease. Some properties such as electronic distribution, size of the molecules, hydrophobicity, binding characteristic, presence of groups responsible for the biological activity of the molecules and flexibility are major influencers and with the ability to modulate the behavior of the molecule in a biological organism including transport properties, bioavailability affinity for proteins, metabolic stability, toxicity and other properties.one of the physiochemical properties is molecular weight which can be a great differential in relation to intracellular processes such as intestinal absorption, penetration in the blood brain barrier (BBB) elimination rate and interaction with molecular targets the analyzed molecule of phenobola showed molecular weight with acceptable variability (216.16g/mol). The acid base of character determined by the ability to accept and donate protons H^+ (lipnisky et al) inferred that molecules that exhibit a lower number of hydrogen bond donor atoms some of hydrogen donor atoms O-Hand N-H

and a higher number of hydrogen bond accepter atoms – sum of hydrogen bond accepter atoms O and N have the most favorable ADME/Tox profile.

The TPSA of the molecule often associated with bonds that the structures is capable of making and which is also involved with modification in oral permeability. This parameter is also used in association with the counting of rotational bonds and allows the analysis of the molecular flexibility acting on the drug likeness profile of the molecule. Considering that the great majority of the active drugs by oral route are passively absorbed having transpose the lipidic layer that constitutes the hydrophilic environment of the biological membranes.

Table 6: Show result of physiochemical properties.

	Physicochemical Properties
Formula	C12H10P2
Molecular weight	216.16 g/mol
Num. heavy atoms	14
Num. arom. heavy atoms	12
Fraction Csp3	0.00
Num. rotatable bonds	0
Num. H-bond acceptors	0
Num. H-bond donors	0
Molar Refractivity	68.05
TPSA	27.18 Å²

CONCLUSION AND RECOMMENDATION

In this study the phenobola drug for Clathrin mediated endocytosis (CME) cycle inhibitor that can be used as treatment of Ebola is a deigned drug using computer software that means it need to apply for clinical research trial (CRT) and more laboratory checking so as to be released into the market and patients get benefit from. This way of drug design become more apply in pharmaceutical companies and in drug and chemical laboratories especially after designed many software and tools that helps in that.

With these predicted pharmacokinetics and chemical properties of phenobola drug make it one of new emerging drug to treat the Ebola disease which, most of African poor countries suffer from, and this can be happen after more laboratory procedure. The drug looks safe and with no harm mentioned according to results outcomes of the predicted software.

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