



## COMPUTER AIDED DRUG DESIGN: TOOLS TO DEVELOP DRUG FOR COVID 19

BISWARANJAN RAY<sup>1\*</sup>, ASHOK KUMAR PANIGRAHI<sup>2</sup>, SULOCHANA DUTTA<sup>3</sup>  
AND MONALISA GOCHAYAT<sup>3</sup>

<sup>1</sup>Department of Pharmacology, CPS, Puri, Odisha, India.

<sup>2</sup>Department of Pharmacology, VIMSAR, Burla, Odisha, India.

<sup>3</sup>GCP, Sambalpur, Odisha, India.

### AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

*Received: 17 July 2021*

*Accepted: 21 September 2021*

*Published: 24 September 2021*

*Review Article*

### ABSTRACT

The CADD includes the combined use of modern computational and experimental techniques which provide structural information about the biologically active molecules. These molecules are involved in disease process and in modulating disease process. The processes of CADD methods are dependent on Bioinformatics tools, applications and database.

The present Review article highlights how the modern computational and experimental techniques that have been developed in recent years can be used together to provide structural information about the biologically active molecules that are involved in disease process and in modulating disease process in Special focus to Drug designing for COVID 19 by virtual Screening.

Out Put of the article: The present article may be one tool for new drug development against corona Virus.

**Keywords:** Bioinformatics; molecular biology; combinatorial chemistry; isolaton; nomenclature.

### 1. INTRODUCTION

The cadd includes the combined use of modern computational and experimental techniques which offer structural data approximately the biologically active molecules. Those molecules are worried in sickness procedure and in modulating sickness procedure.

The theoretical basis of cadd includes the quantum mechanics and molecular modeling research like shape based drug design, ligand primarily based drug design, database looking and binding affinity based on the organic goal [1].

The fee gain of the use of computational gear within the lead optimization phase of drug development is considerable. The value and time invested by means of the pharmacological studies laboratories are heavy at some stage in the numerous section of drug discovery, starting from healing target identification [2].

The decrease stage contribution represents the alternative of crude mechanical fashions by means of presentations of shape, capable of demonstrating motion and solvent impact.

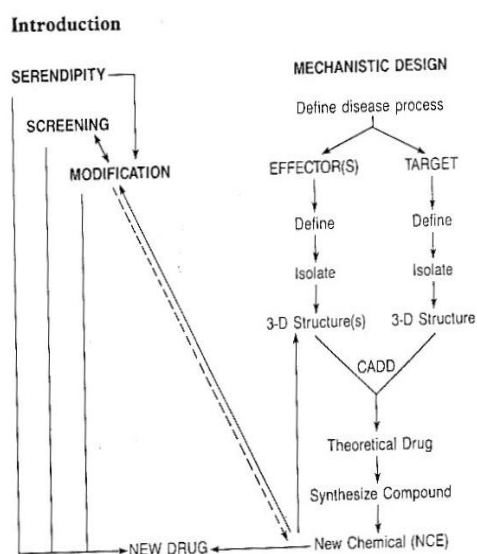
Awesome classes of research are truly distinguishable-

\*Corresponding author: Email: crabiswa@gmail.com;

1. Crystallography, nmr or homology modeling. A detailed molecular structure of the goal macromolecule, the receptor is understood from x-ray.
2. Variable hobby of otherwise similar molecules. The goal receptor binding website online has houses that can simplest be inferred from understanding of each those forms of approach.

### Drug discovery

The drug discovery is the series of technique for perceive the drug compounds for effective remedy. It requires whole records about structure of drug receptor so that drug molecule attach to the binding web site.



#### •screening for brand spanking new drug:-

Screening of a big variety of synthetic chemicals or natural products for ideal results is the traditional manner to discover new tablets.

However the largest disadvantage of this procedure is requirement for the precise technique. Although the drugs are ultimately advanced inside the medical institution, it's also inappropriate to chemicals of acknowledged efficacy without delay into humans.

Number one screening is used for large variety of chemical substances to choose which compounds ought to be similarly tested.

The secondary screening is carried out inside the animal model system. The screening method is inherently repetitious and time consuming just to find chemical with preferred interest [3].

#### Steps of drug design:-

1. Candidate for drug discovery-
  - A. Choice of therapeutic target
  - B. Lead discovery
  - C. Lead optimization
2. Preclinical and clinical trials to assess the safety, efficacy and negative effect of drug
  - A. Animal studies
  - B. Clinical trial
3. Fda popularity of newly observed drug
  - A. Additional put up advertising and marketing checking out
  - B. Similarly development of drug

In standard, it takes 3-6 years to form preclinical trial. The scientific trial lasts up to 10 years or greater earlier than it reaches the market [4]. Approximately 12-15 years required to bring a a hit drug to the market [5].

#### Computer aided drug designing: a new method

Two distinct methods are viable within the region of cadd. If the shape of target macromolecule is understood, the strategies are apparent and direct. While the most effective lead is a set of regarded energetic compounds of a biochemical transformation that is to be interrupted, then the path is less direct.

#### Makes use of of cadd-

### 1. Crystallography –

Primary aim of chemical crystallography is to supply a fixed of coordinates defining the places of atoms in a molecule. It is very much useful in the method of deciphering crystal structure.

Based on enter from the cambridge crystal report, which includes crystal coordinates for over 50,000 compounds [7].

The reason of this programme is to research the type of intermolecular interplay that a molecule chooses when forming a crystal.

The version for drug-receptor interaction is an extension of the lockkey model for enzyme-substrate interaction.

While each the drug and its receptor are known, molecular modeling of the bimolecular complicated should be done.

## 2. Receptor mapping-

once one has a set of medication that every one are fantastically active, one can hypothesize that the overlap of all molecules defines a quantity that the receptor need to be capable of accommodate [8].

The receptor has flexibility in geometry. The surface that is inferred from the overlap of the energetic molecule is referred to as a receptor map.

A chain of drug compound is suggested based at the concept that an energetic drug need to comprise certain pharmacophoric corporations to have pastime. [9]

Gain of this kind is that it can be constantly delicate as greater energetic drugs are discovered. Drawback is that it's far uncertain about the conformation of drug molecule.

## 3. Molecular mechanics and dynamic's-

Graphics is used to prepare input structure for these programs and to look at the resulting structures. These are the statistical ways of analyzing results to give free energies, entropies etc.

Even though it may be difficult to express these conformational results in a way that would be easy to graph (as a dihedral angle plotted against time) the chemist looking at conformations on a computer graphics screen can categorize them and detect important conformational transitions. These conformations are used in many ways i.e. molecular mapping, rotation of bonds etc.

## 4. Nuclear Magnetic Radiation (NMR)-

The best technique to obtain good crystals and three dimensional data obtained with crystals under biological condition is the NMR spectroscopy. The basis of the experiment is distance between the specific hydrogen atoms in a molecule. [10]

## 5. Molecular docking, surface and hydrogen bond-

Molecular docking anticipates the favored orientation of ligand against receptor to make a stable complex. The long-range forces responsible for guiding two molecules together into the docked conformations are not the suitable minimization method. The process of interactive docking was hindered by the need to use separate devices to control separate graphical operations. Since that time, a 3-D tracking device was incorporated into the CAMD system.

## 6. Quantum mechanics-

It offers a better description of electronic structure than molecular mechanics can ever do. The parameters used for force fields in molecular mechanics and dynamics are often computed using quantum mechanics method [11].

Computer graphics can even be of use in this way, by analyzing and assigning normal modes of vibrations from quantum mechanical results. Graphical analysis greatly speeds this analysis. In some studies of structure-activity relationships for drug molecules, it has been shown that the energy of the highest occupied molecular orbital for a molecule correlates with the drug activity [12]. A true three dimensional contour is possible using interactive computer graphics.

## 2. MOLECULAR MODELING SYSTEM FOR DRUG DESIGN

This includes a wide variety of features such as statistical packages for QSAR, programs for molecular mechanics and dynamics calculations and quantum mechanical programs. This provides possible target proteins for drug screening and designing. As a supplement to experiments, protein structure prediction method can provide protein structures with reasonable precision. Bimolecular stimulations with multiscale models are useful for identifying drug binding sites and elucidating drug action mechanisms.

Molecular docking, which predicts interaction patterns between proteins and small molecules as well as proteins and proteins, to evaluate the binding between the two molecules is widely used in the field of drug screening and designing. The theoretical basis is that the process of ligand and receptor recognition relies on spatial shape matching and energy matching, which is the theory of "inducing fit". Determining the correct binding conformation of small molecule ligands and protein receptors in the formation of complex structure is the basis for drug designing and studying its action mechanics.

### 2.1 The camd gadget

The molecular modeling responsibilities were performed using the computer assisted molecular design (camd) gadget. Readers who aren't familiar with molecular modeling systems can use the outline of the camd machine as a widespread indicator of what these structures are capable of doing. Readers with more enjoy with molecular modeling machine can use the description to evaluate analogous functions and productiveness amongst structures.

Camd is made from numerous pieces that are related in distinctive methods. It uses gramps to do its photos. Gramps, a standard motive snap shots application for display of arbitrary graphical gadgets; pds, a protein modeling machine; cmd, a small molecule modeling gadget; a small molecule modeling machine; and engage, a program to coordinate records switch among gramps/cmd/pds and offer a convenient person interface. Cmd, pds and engage are linked collectively and speak to gramps the use of the vax/vms mailbox facility for inter manner communicate [13].

Spherically shaped, plastic pieces. They may be manipulated to provide diverse conformation of the molecules [14].

The bond lengths and bond angles can't be adjusted in those models. Deriding models are physical fashions that use skinny metallic or plastic rods to symbolize bonds. Bond lengths and angles are constant, despite the fact that rotations around bonds may be without problems carried out.

Computers photos fashions can also very readily be used to represent digital houses of molecules. These fashions may be appropriately built using bond lengths, bond angles and torsion angles. The drawback of this model is that they're no longer physical, 3-dimensional fashions. Typically, the fashions are drawn on a cathode-ray tube (crt), the usage of unique cause computer hardware.

Laptop pix systems along with the ps350 and the silicon pics iris work station permit combining the strategies [15].

### **I. Vector as opposed to raster system:-**

Computer images shows are both 'vector or raster'. On vector displays, the lines making up the photograph are traced at the face of the crt. The traces are continuous strokes and appear very instantly and easy. On raster displays, the crt is repeatedly horizontally scanned, as on a television screen. The photograph is made from discrete pixels. Traces can appear jagged, depending on the decision of the crt getting used.

The evans and sutherland ps390 is a raster system with line-drawing capabilities as good as on vector systems. [16]

### **II. Computer:-**

Workstations are the raster structures in which a pc with a full working gadget and mass storage facility is included with the graphical display. Ex- silicon

pictures iris, solar photographs workstations and apollo workstations.

## **2.2 Computed Molecular Models**

The principle cause of molecular modeling is so that it will represent a few aspects of molecular shape using a laptop graphical version. The two critical aspects of molecular shape are, the first one is the atomic connectivity and atom sorts and second one is the extent and/or form of the molecules. The other aspects encompass alpha carbon plots, ribbon diagrams to symbolize protein shape [17].

## **2.3 Molecular Stick Figures**

It's far the most familiar pc molecular version. But this technique calls for a large amount of computer time which will increase exponentially because the range of bonds increases. The usage of interactive actual time graphics, you can actually assign dials to rotate molecular sections round one or greater bonds. The gain of interactive graphics isn't always in producing masses of configurations or in ruling out conformation. The drug does now not act on my own. It requires a receptor for its pharmacological impact to be expressed. But calculating the distance and overlapping of molecules is hard on this model.

## **2.4 Molecular Surfaces**

The general concept of molecular floor changed into proposed by way of lee & richards. If one imagines the molecule to be made of spheres of appropriate sizes, the superposition of all these spheres might supply rise to the molecular floor and extent much like a cpk version of a molecule. The solvent-available to solvent is the part of the molecular surface this is on hand to solvent. The small cervices between the atoms are not reachable to solvent. On this technique, whilst the probe sphere just touches an atom sphere, factors are generated to record the solvent accessibility of that atom. These surfaces deliver a terrific representation of the shape and volume occupied by means of a molecule [18].

## **2.5 Coloration-coded Surfaces to Symbolize Molecular Houses**

You'll colour the dots to expose which sort of atom they belong to. This can assist in visible evaluating of a set of molecules to come across wherein and the way they're similar or one-of-a-kind. The useful property that is frequently used to shade-coded surfaces is electrostatic capacity electricity. If every atom in a probe sphere consists of a unit nice price,

then you can still easily compute the coulomb electrostatic capability strength. If the electricity is bad, then the surface dot is coloured pink. If it's miles zero, then the dot is colored green. If it's miles nice, then the dot is coloured blue. The overall model of drug-receptor interplay is equivalent to the lock-key model of enzyme-substrate interactions.

## 2.6 Other Molecular Properties

One assets effects from a quantum mechanical calculation on a molecule is the electron density. This amount has a particular value at every factor in area surrounding the molecule. If one collects together factors of identical value, a contour of identical electron density outcomes. In the other manner, the electron density is a surface of constant electronic nature with the shape variable consistent with the scale of electron cloud close to that factor in area across the molecule. Both instances constitute the capacity of a molecule to use its electrons to interact with every other molecule. Inside the electrostatic potential electricity color-coded floor, the colour shows the interaction at a set place. The electron density contour suggests how a long way a given fee of electron density can reach out closer to every other molecule to interact with it [19].

## 2.7 Other Molecular Representations

For big molecules like proteins, drawing a entire stick parent displaying each bond consequences in a photo that is too cluttered and not very informative. One method of representing proteins that enables keep away from muddle is an alpha carbon plot. Due to the fact the regularity of polypeptides, each amino acid can be represented through its alpha carbon. The positions of those atoms are linked with the aid of pseudo bonds. The overall shape of the protein can be conveniently visible, and the point at which the facet chain emerges from the principle chain is smartly depicted as well. As molecules come to be even large, even more schematic representations are vital. A virus is a set of macromolecules, normally with a protein outer coat. Several viruses had been crystallized and plenty of information in their shape have been found out. The tomato hairy virus (tbsv) has an outer coat which includes a hundred and eighty almost identical proteins organized on an icosahedrally symmetric shell [20].

## 2.8 Different Packages of Laptop Aided Drug Designing

1. Computer aided designing and assessment of angiotensin converting enzyme inhibitors
2. Role within the design of novel inhibitors of renin

3. Inhibitors of dihydrofolate reductase
4. Antiviral drug designing
5. Conformation biological pastime relationships for receptor selective, conformationally, constrainedopioid peptides
6. Layout of conformationally limited cyclopeptides for the inhibition of cholate uptake of hepatocytes .

## 2.9 Benefits of Laptop Aided Drug Designing

### 1. Cost saving-

The price of discovery and development has reached \$800 million for every drug successfully brought to marketplace. Now-a-days many biopharmaceutical companies are the use of the computational techniques and bioinformatics tools to reduce their cost burden.

Virtual screening, lead optimization and predictions of bioavailability and bioactivity can assist guide experimental studies. Simplest the most promising experimental strains of inquiry can be followed and experimental lifeless-ends can be averted early primarily based on the results of cadd simulations.

### 2. Time to marketplace-

The predictive electricity of cadd can help drug studies packages choose most effective the most promising drug applicants. Via focusing drug studies on specific lead applicants and fending off ability 'useless-ends' compounds, biopharmaceutical corporations can get capsules to marketplace more speedy.

### 3. Insight

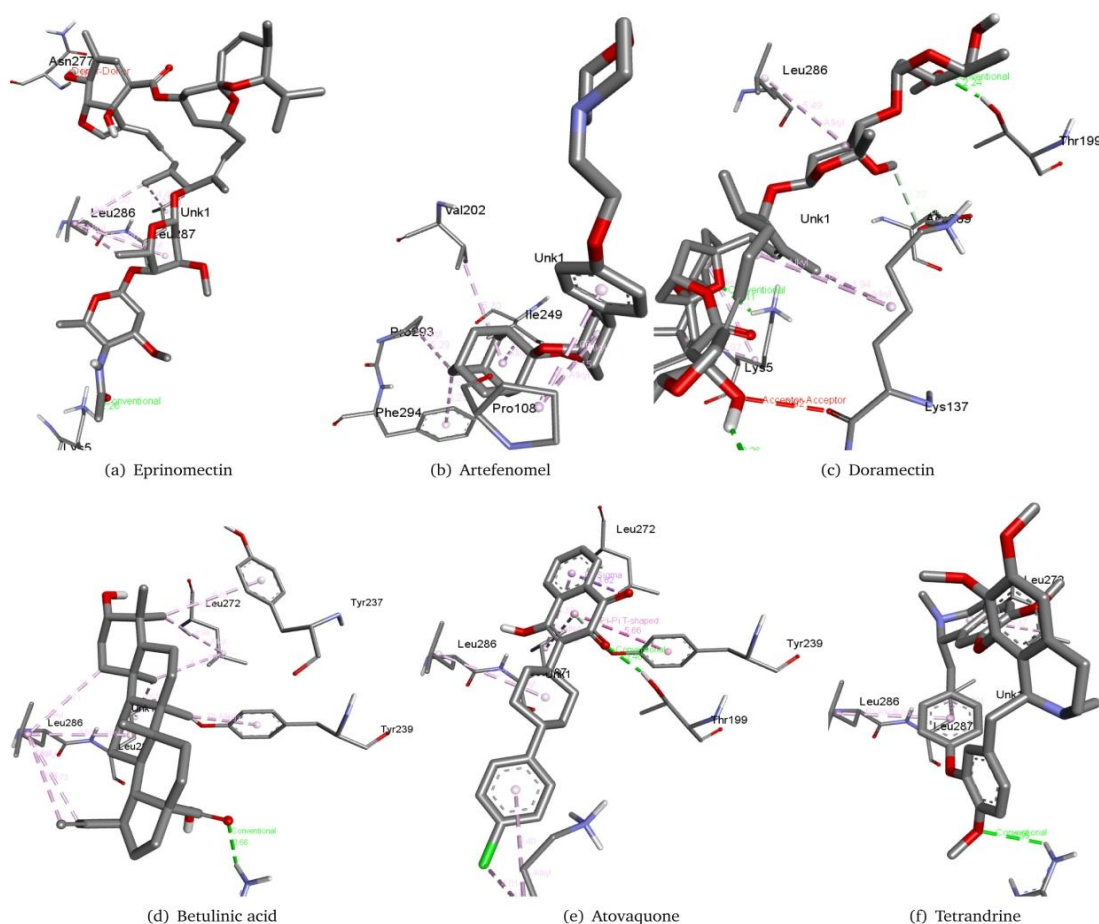
One of the non-quantifiable advantages of cadd and use of bioinformatics gear are the deep insight that allows approximately take a look at of receptor interaction. Molecular models of drug compounds can screen complicated, atomic scale binding residences that are hard to check in another manner. Cadd and bioinformatics collectively are a effective mixture in drug research and development.

## 2.10 Capsules for Covid-19 Virus Designed by Way of Cadd

With the non-stop upward thrust in wide variety of confirmed cases for the reason that outbreak of the sars-cov-2, a fast and reliable tool which include laptop aided drug layout (cadd) is of the essence. Due to the current emergent of the corona virus ailment, there aren't MANY crystal structures of high

resolution of the virus. As on the time the majority of this paintings was finished, there was no crystal structure of the spike protein. Subsequently, homology modeling become employed. However, as at the cease of march 2020, there are presently about one hundred crystal structures of the sars-cov-2 deposited in the protein databank. The mcule complete database with precisely 44,704,142 compounds, as at that the time of this work, become used for the primary digital screening test. A blind docking changed into completed, which blanketed the entire of the protein on account that no binding pocket has been determined from experiments yet with the Following parameters -1.298, -7.617 and 191.965 for x, y and z axes respectively. These coordinates constitute the binding web page location. The mcule database became filtered the usage of drug-like properties as utilized in our in advance works which consist of having a most of five halogen atoms, 5 chiral centres and ten rotatable bonds; not less than 10 heavy (non-hydrogen) atoms and at the very least 1

aromatic ring; and finally should now not violate now not extra than one of the lipinski's rule of five (ro5). After the filtration, a hundred,000 compounds had been screened randomly using autodock vina as the molecular docking device. The variety choice of those 100,000 compounds for a 2d digital screening with bindscope. To use bindscope, the target protein, the homology modeled structure of the spike protein of sars-cov-2 in this example, became uploaded in pdb to the internet application alongside a hard and fast of docked ligands (on this Case the pinnacle 500 scored ligands from the first digital screening) in shape-records file (sdf) layout. The results from the virtual screenings have been mixed for consensus scoring the usage of the rank vote casting technique to choose the compounds which regarded as pinnacle-scored in each digital screenings. The floor glycoprotein for sars-cov-2 is made from 1273 amino acids at the same time as the sars-cov is 1255. The sars-cov-2 is 76% Identical to the sars-cov [21].



### 3. INTERACTION OF COVID-19 MAIN PROTEASE 6M03 WITH LIGANDS

Some of the Molecular modeling systems available are:-

AMBER: Molecular mechanics and Dynamics, Department of Pharmaceutical Chemistry, University of California

FRDOX: Molecular Display (especially macromolecular Crystallography) Dr.Flo Quichocho, Department of Chemistry, Rice University.

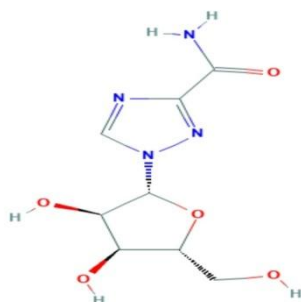
### 4. DRUGS DESIGNED BY VIRTUAL SCREENING FOR COVID-19

#### A. RIBAVIRIN:

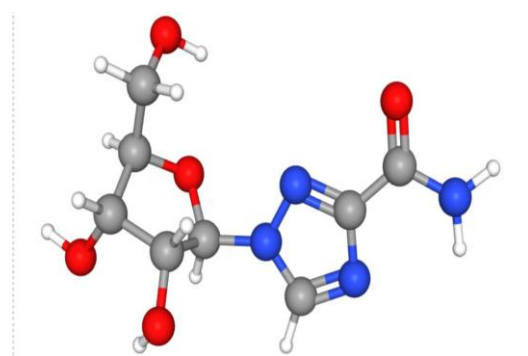
Ribavirin at the same time known as potent drugs against SARS-COV-2. Since they tightly bind to it's RdRp. It is a synthetic guanosine nucleoside and antiviral agent.

It's molecular weight is 244.2g/mol, physical appearance is white powder, melting point is about 174-176°C and soluble in water and slightly soluble in alcohol [22].

#### 2D STRUCTURE:



#### 3D STRUCTURE:



### IUPAC NOMENCLATURE

1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1H-1,2,4-Triazole-3-carboxamide.

#### Mechanism of Action

Ribavirin converts into its active metabolites i.e. Mono-, di- and tri- phosphate metabolites with the assist of adenosine kinase enzyme. While ribavirin triphosphate binds to the nucleotide binding web site then it inhibits the viral mrna polymerase. There by means of binding of accurate nucleotides is prevented and there is lower in viral replication and manufacturing of faulty virion.

While ribavirin have interaction with corticosteroids with sars-cov pneumonia resulted in resolution of fever and lung opacities within 14 days [23,24,25]. whilst ribavirin interacts with interferon  $\beta$ , inhibits then it inhibits sars-associated corona virus replication in vitro. Ribavirin, whilst used synergistically with interferon 1  $\alpha$  and interferon  $\beta$  then it suggests antiviral activity in opposition to sars corona virus [26,27] ribavirin used with interferon  $\alpha$  in mers-cov led to development in 4 days in one affected person and 6 days in another [28] this purine nucleoside analogue has huge spectrum antiviral interest which inhibits viral rna synthesis, thereby can be used for covid-19 [29] it has additionally been recommended to apply for covid-19 thru intravenous infusion [30] then stops the polymerase function [31] by way of tightly binding with sars-cov-2 rdrp. Furthermore ribavirin ought to be used in mixture with either interferon or lopinavir or ritonavir to enhance its antiviral interest against sars-cov-2.

#### Pharmacology

Ribavirin is a purine nucleoside analogue. Despite the fact that its mechanism of movement is still debated, it prevents replication of a huge range of rna and dna viruses through inhibiting the enzyme inosine monophosphate dehydrogenase, which is required for the synthesis of guanosine triphosphate. The very last step in this chain of occasions is deadly mutagenesis of the rna genome. In vitro inhibition of rsv, influenza viruses and parainfluenza viruses is executed at ribavirin concentrations of 3-10  $\mu\text{g/ml}$ .

The plasma elimination of ribavirin happens in 2 phases, the primary with a fairly short half-of-existence of 2 hours, the second with a much longer terminal half-of-life of sixteen–164 hours. The lively metabolite of the drug, ribavirin triphosphate,

concentrates in erythrocytes and leaches out slowly, with a 1/2-existence of forty days. Ribavirin has 2 metabolic pathways: a reversible phosphorylation pathway and a degradative pathway related to deribosylation and amide hydrolysis. Ribavirin is removed typically with the aid of renal excretion, and dose reductions are required in patients with renal insufficiency [32].

#### Molecular system:

C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub>

#### Efficacy of Ribavirin in Sars

There are numerous methodological problems in these early reviews that ward off any conclusions approximately the efficacy of ribavirin in the treatment of sars. Given that the putative causative agent is a new pressure of coronavirus that has not formerly affected human beings, it'll be essential to reap extra records at the in vitro susceptibility of this virus to ribavirin and other investigational and licensed antivirals. The us food and drug administration has initiated this type of screening software.

Until extra statistics turns into to be had at the efficacy of ribavirin and the optimum control sars, it's far probable that use will continue to be advocated at the least in a subset of sicker sufferers. Canadian physicians ought to turn out to be familiar with the contradictions to ribavirin use and the established unfavourable results of the drug and ought to closely monitoring sufferers receiving ribavirin for as-but-undescribed quick-term and long-term negative occasions.[33]

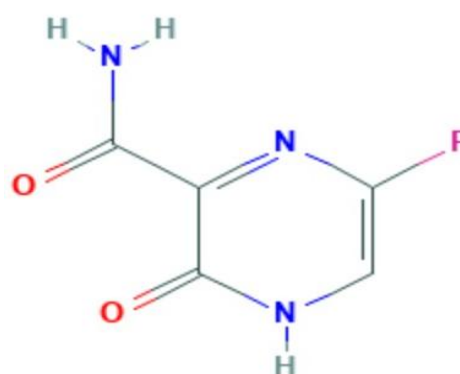
#### B. Favipiravir

Favipiravir, formerly referred to as t-705, is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5'-triphosphate. It has shown speedy viral clearance and faster medical development. Favipiravir is converted to the ribofuranosyltriphosphate by-product by host enzymes and the lively agent inhibits the influenza viral rna –dependent rna-polymerase, stumbling viral replication. It's miles an oral broad spectrum rdrp inhibitor and in step with in-vitro studies, favipiravir will have an effective awareness against the sars-cov-2 infection inside a secure healing dose.

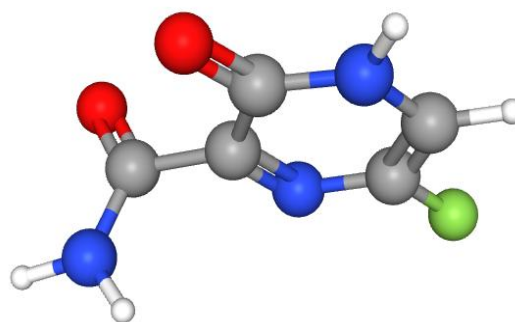
#### MOLECULAR FORMULA:

C<sub>5</sub>H<sub>4</sub>FN<sub>3</sub>O<sub>2</sub>

#### 2D STRUCTURE:



#### 3D STRUCTURE:



#### IUPAC NOMENCLATURE:

6-fluoro-3-hydroxy-2-pyrazinecarboxamide

#### MECHANISM OF ACTION

Favipiravir is a prodrug which is a purine based analog. After administration, this drug undergoes phosphoribosylation and converted into active favipiravir ribofuranosyl-5B-triphosphate (Favipiravir RTP) and exerts its antiviral effect through following mechanism.

- Favipiravir RTP is a selective and potent inhibitor of RdRp of RNA viruses and prevents replication of viral genome.[34]
- Favipiravir RTP is incorporated into nascent viral RNA strand, by error viral RdRp which results to chain termination and viral mutagenesis.[35,37]
- Although favipiravir was originally developed to treat influenza, the catalytic domain of RdRp exiting various types of RNA viruses explains a broad spectrum of antiviral activities of favipiravir.[36,37]



- It has recently been shown that after RNA viral incorporation favipiravir-RTP works like mutagen which is capable of emigrating corona virus repair machinery so called as virucidal drug. [38]

### SAR OF FAVIPIRAVIR

- Modified 2'-C-methyl-NTP analogs gives rise to immediate chain termination.
- Essential benzene rings and pyrrolidinone scaffold are claim for proper binding with VP35.[39]
- Smaller compounds with pyrazine ring are docked deeper but relatively smaller pocket of VP3.

### C. LOPINAVIR/RITONAVIR

The combination of lopinavir and ritonavir is considered to be a highly effective antiretroviral agent. This combination showed better virological eradication and radiological improvement with a reduced rate of ARDS as compared with other anti-

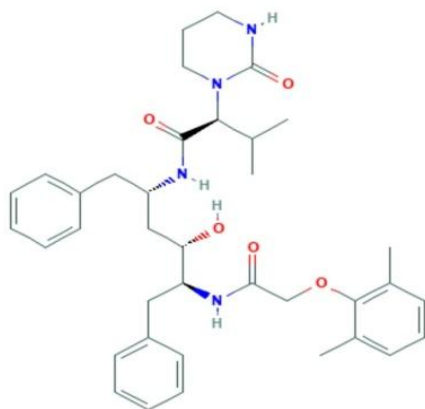
corona virus agents[40] and has been suggested as an anti-viral treatment for COVID-19,[41] a deadly respiratory infection pandemic caused by the SARS-nCoV-2 virus. Lopinavir (LPV) is a HIV-1 protease inhibitor, which is combined with ritonavir to increase its plasma half life. LVP is also an inhibitor of severe acute respiratory syndrome corona virus (SARS-COV) protease.[42] Ritonavir also a protease inhibitor which is administrated in combination with lopinavir to enhance its bioavailability by inhibiting its metabolic inactivation. LVP is usually given in combination with low booster doses of ritonavir which increases the pharmacokinetics of LVP by slowing its hepatic metabolism through the inhibition of cytochrome P450 3A4 enzyme.

This combination has invitro inhibitory activity against-

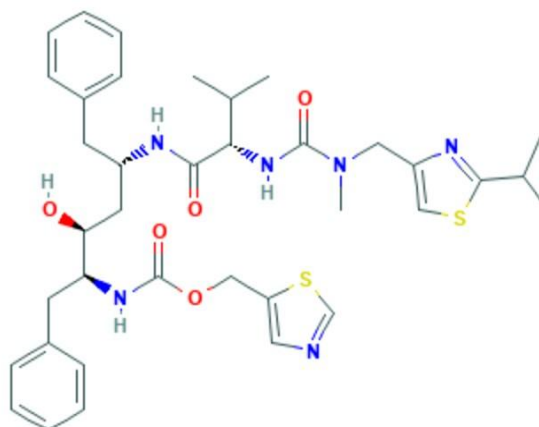
- SARS-CoV
- SARS-CoV-2
- Middle East Respiratory Syndrome (MERS) corona virus[43,44,45]

### 2D STRUCTURE:

#### LOPINAVIR



#### RITONAVIR



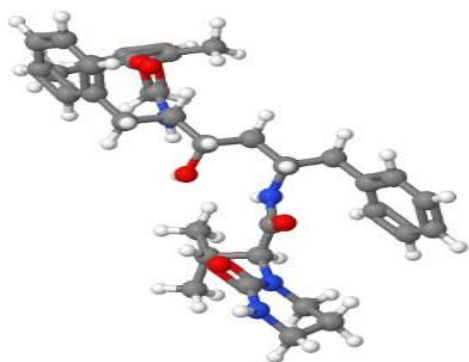
#### IUPAC NOMENCLATURE OF LOPINAVIR

(2S)-N-[(2S,4S,5S)-5-[[2-(2,6-dimethylphenoxy)acetyl]amino]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide

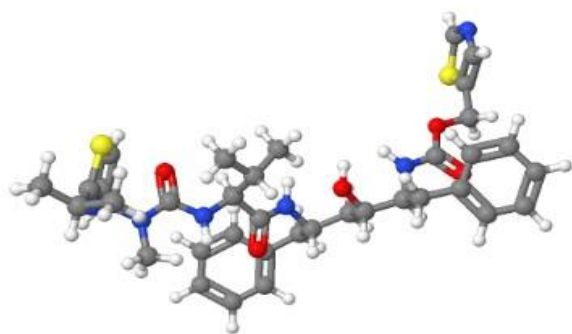
#### IUPAC NOMENCLATURE OF RITONAVIR

1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[(2S)-3-methyl-2-[[methyl({[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl})carbamoyl]amino]butanido]-1,6-diphenylhexan-2-yl]carbamate

### 3D STRUCTURE OF LOPINAVIR:



### 3D STRUCTURE OF RITONAVIR:



### MOLECULAR FORMULA OF LOPINAVIR:

C<sub>37</sub>H<sub>48</sub>N<sub>4</sub>O<sub>5</sub>

### MOLECULAR FORMULA OF RITONAVIR:

C<sub>37</sub>H<sub>48</sub>N<sub>6</sub>O<sub>5</sub>S<sub>2</sub>

### MECHANISM OF ACTION

Lopinavir / ritonavir may be considered for use as part of an investigational protocol for patients with COVID-19.

- SARS-CoV-2, is a single stranded RNA  $\beta$  corona virus which is similar to SARS-CoV and MERS-CoV.
- These viruses enter into the host cell and then replicate to form RNA with the help of enzyme 3-chymotrypsin-like protease (3CL pro). [46,47]
- This strand of genetic material accumulates at the periphery of the cell and then starts to be cleaved, packaged and prepared for release from the host cell. [48]

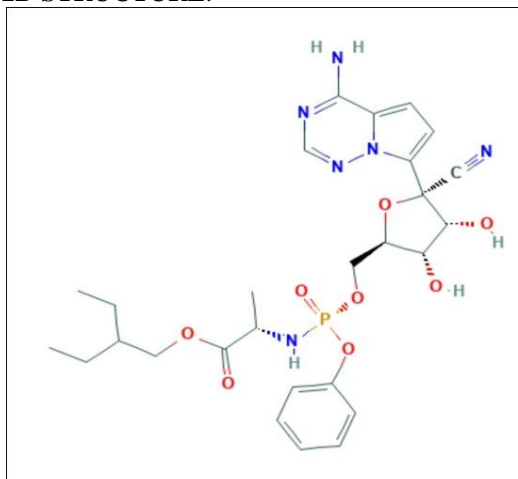
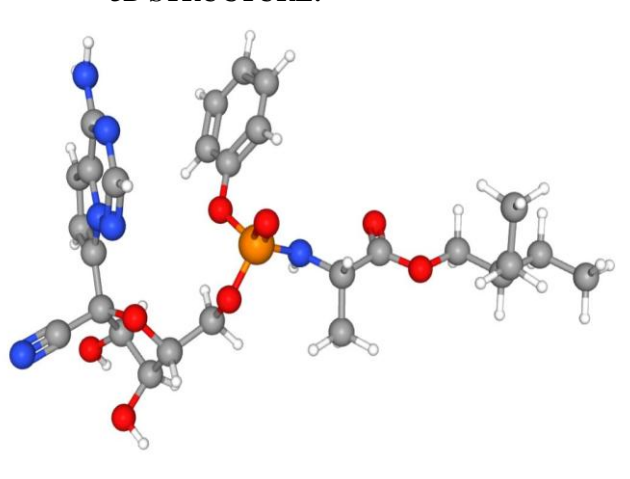
- LPVr is a protease inhibitor. So that it inhibits the action of 3CL pro which causes disruption of the process of viral replication and release from the host cell. [46,47]
- Main antiretroviral effect due to lopinavir/ritonavir inhibits metabolism to prodrug action/increase serum concentration.
- Recent evidence suggests that lopinavir has antiviral activity against SARS-CoV-2 in vitro. [49]

### SAR OF LOPINAVIR/RITONAVIR

- Substituted groups on the A1 aromatic rings have influence on their biological activity.
- Substituted groups on the A2 ring are also important for good antiviral property. [50]

### D. REMDESIVIR

Remdesivir is a prodrug of an adenosine triphosphate (ATP) analogue, with potential antiviral activity against a variety of RNA viruses. It is an antiviral nucleotide analogue used for the therapy of severe novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) infection. [51]

**2D STRUCTURE:****3D STRUCTURE:****MOLECULAR FORMULA:**C<sub>27</sub>H<sub>35</sub>N<sub>6</sub>O<sub>8</sub>P**IUPAC NOMENCLATURE:**

2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxoxolan-2-yl]methoxyphenoxyphosphoryl]amino]propanoate.

**MECHANISM OF ACTION**

COVID-19 is caused by the positive-sense RNA virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Remdesivir is a phosphoramidite prodrug of a 1'-cyano-substituted adenosine nucleotide analogue that competes with ATP for mixing into newly synthesized viral RNA by the corresponding RdRp complex. It goes cells before being cleaved to its monophosphate form through the action of either carboxyl esterase 1 or cathepsin A [52].

**ROUTE OF ELIMINATION**

Remdesivir is 74% wiped out in the urine and 18% wiped out in the feces. 49% of the recovered dose is in the form of the metabolite GS-441524, and 10% is recovered as the unmetabolized parent compound. A small amount (0.5%) of the GS-441524 metabolite is found to be present in feces [53].

**PHARMACOLOGY**

Remdesivir is recommended for the treatment of adult and paediatric patients aged 12 years and over weighing at least 40 kg for coronavirus disease 2019 (COVID-19) infection requiring hospitalization.

Under this indication, remdesivir should only be administered in a hospital or other healthcare setting capable of providing acute care comparable to an inpatient hospital setting [54].

**4.2 Application of Remdesivir**

**Summary of Antiviral Activity Against Different Viruses:** Remdesivir (GS-5734) was developed by Gilead Sciences. Gilead, the US Centers for Disease Control and Prevention (CDC) and the US Army Medical Research Institute of Infectious Diseases (USAMRIID) collaborated to discover drug candidates against RNA viruses with potential to induce a global pandemic (eg Ebola virus, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) coronaviruses). In order to find suitable antiviral agents against the RNA viruses, a library of approximately 1000 reworking nucleosides including monophosphate, ester and phosphoramidate prodrugs was compiled. Results of data screening showed that GS-441,524 (a 1'-CN modified adenosine C-nucleoside hit) along with GS-5734 (a prodrug form of the monophosphate of GS-441,524, later renamed as remdesivir) were highly potent antivirals [55].

In 2020, de Wit et al studied the prophylactic and therapeutic activities of remdesivir against MERS in rhesus macaques (a nonhuman primate model). Results showed that the viral load in the lungs of the treated animals was lower than that of the controls. The severity of lung lesions in the therapeutic treatment group was lower than that in the vehicle-treated animals. The lungs of the prophylactically treated animals were normal. Taken together, the results emphasized the efficacy of remdesivir as a prophylactic and therapeutic agent against MERS [56].

In 2020, Sheahan et al showed that remdesivir and interferon-beta have a superior antiviral activity compared to lopinavir and ritonavir against MERS-CoV in vitro. In mice, both prophylactic and therapeutic remdesivir improved the respiratory function and decreased the pulmonary viral loads and severe lung pathology. In contrast, prophylactic lopinavir/ritonavir-interferon beta somewhat reduced the viral loads without affecting other disease factors. Therapeutic lopinavir/ritonavir-interferon beta increased pulmonary function but did not decrease virus replication or severe lung pathology. Overall, the authors suggested that remdesivir might improve the disease outcomes in coronavirus-infected patients, be useful to protect health care workers in regions with endemic MERS and inhibit future coronavirus epidemics [57].

#### E. TENOFOVIR/EMTRICITABINE

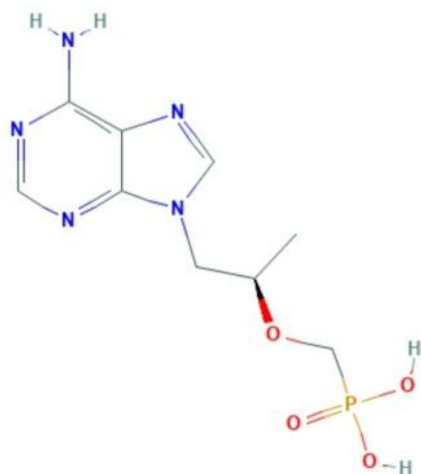
This is a well known antiretroviral agent having characteristics such as high barrier resistance, long plasma and intracellular half life. According to WHO, tenofovir and emtricitabine are considered as

indispensable medicines which are the nucleot(s)ide analogues.[58] It has the potential activity against RdRp,[59,60,61]an enzyme which is essential for SARS-CoV-2 replication. So, it has the potential to inhibit SARS-CoV-2 replication, [62,63,64,65] which could play a role as chain terminator, has been supported by in vitro [66] and in vivo [67] experiment. Thereby, this combination can be used as a permanent terminator for the SARS-CoV-2 RdRp enzymatic function. The combination of tenofovir, emtricitabine and lamivudine is used as post exposure prophylaxis and treatment for HIV infection in adults and adolescents and other viral infections.

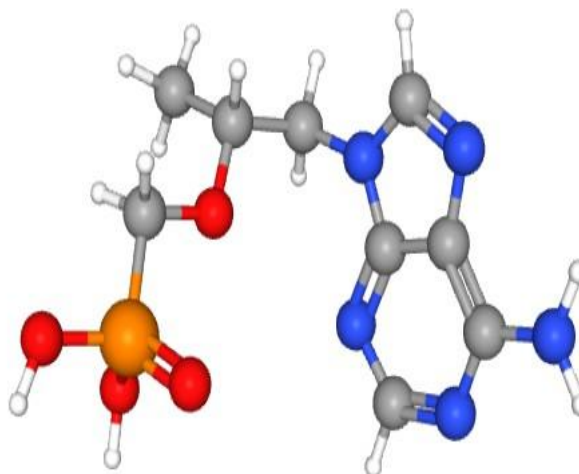
According to experimental studies, the main goal of this combination is to evaluate the effectiveness of a drug to stop the infection with the virus that causes COVID-19 (SARS-CoV-2) in health care workers. As reported by recent studies, tenofovir may also play a good role in the treatment or prophylaxis against COVID-19. Also proved that risk of COVID-19 and related hospitalization is lower among HIV positive patients receiving TDF/FTC.[68].

#### TENOFOVIR:

##### 2D STRUCTURE:



##### 3D STRUCTURE:



#### IUPAC NOMENCLATURE:

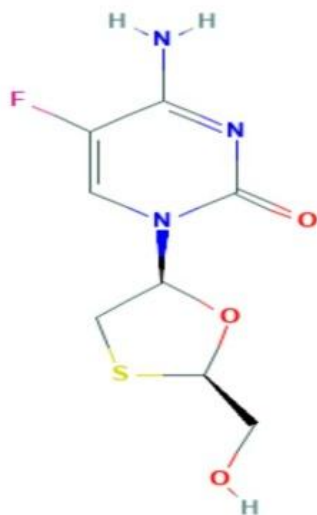
[(2R)-1-(6-aminopurin-9-yl)propan-2-yl]oxymethylphosphonic acid

#### MOLECULAR FORMULA

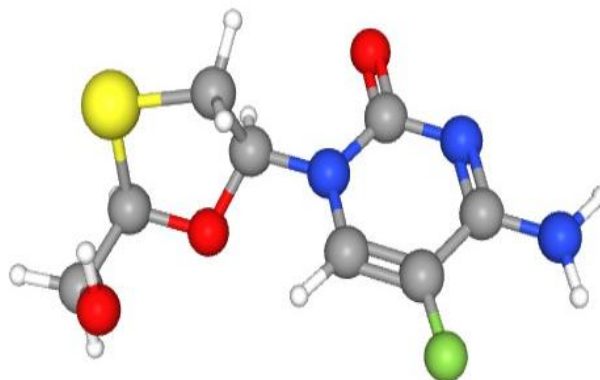
C<sub>9</sub>H<sub>14</sub>N<sub>5</sub>O<sub>4</sub>P

**EMTRICITABINE:**

**2D STRUCTURE:**



**3D STRUCTURE:**



**IUPAC NOMENCLATURE**

4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2-one

**Molecular formula:**

C<sub>8</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>3</sub>S

**Mechanism of action**

**Tdf:**

- fumarate salt of prodrug for tenofovir disoproxil which is nucleotide analogue reverse transcriptase inhibitor, has additionally been hypothesized to be effective in covid-19. [69]
- tenofovir disoproxil is absorbed and converted to tenofovir, active shape of tenofovir disoproxil.
- tenofovir then exchange to energetic metabolite i.e. Tenofovir diphosphate which is a sequence terminator.
- tenofovir diphosphate inhibits hiv-1 reverse transcriptase and hepatitis b polymerase.
- tenofovir display less adverse impact or drug-drug interaction construct it a terrific option for preexposure prophylaxis.[63]
- tdf drastically reduced sars-cov-2 particle production in a cell tradition have a look at via attention among 3 and 90µm.[70]

**Emtricitabine:**

- cytosine nucleoside analogue.

- inhibit hiv opposite transcription.
- thereby, it prevents transcription of hiv rna into dna.

**Tenofovir/emtricitabine:**

- tenofovir / emtricitabine are vital drug treatments which can be the nucleot(s)ide analogues.
- they have the potential to inhibit sars-cov-2 replication.
- nrtis (nucleotide/ nucleoside reverse-transcriptases) consisting of tenofovir and emtricitabine may showcase a prophylactic function towards sars-cov-2 contamination, in view that nrtis have proven binding affinity to most important enzymes of sars-cov-2 in molecular, in vitro, and in vivo research.
- this aggregate is used to deal with hiv, hbv and to prevent hiv contamination as preexposure prophylaxis.

**F. Saquinavir**

Saquinavir is a peptide spinoff which inhibits the hiv protease enzyme, preventing put up-translational processing of viral polypeptides. It changed into the first agent of its magnificence to grow to be available for the treatment of hiv infection. Well managed research have assessed the outcomes of saquinavir, when used alone or in mixture with opposite transcriptase inhibitors, in patients with superior hiv infection [71].

Primarily based on this analysis, it's far clean that each saquinavir recognized to own potent antiviral

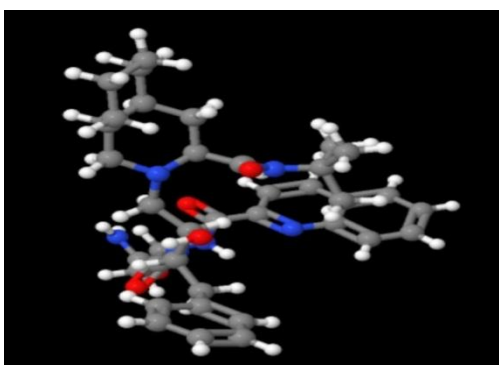
protease inhibitory interest are appealing anti-covid-19 scientific drug applicants [72].

### Molecular formulation:

C38h50n6o5

### 2d shape:

### 3D STRUCTURE:



### IUPAC NOMENCLATURE:

(2*S*)-*N*-[(2*S*,3*R*)-4-[(3*S*,4*aS*,8*aS*)-3-(*tert*-butylcarbamoyl)-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-isoquinolin-2-yl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinoline-2-carbonylamino)butanediamide.

### MECHANISM OF ACTION

The HIV lifecycle is comprised of 3 distinct stages: assembly, involving creation and packaging of essential viral components; budding, wherein the viral particle crosses the host cell plasma.

Membrane and forms a lipid envelope; and maturation, wherein the viral particle alters its structure and becomes infectious. At the centre of this lifecycle is the gag polyprotein which, together with the goods of its proteolysis, coordinate those tiers and characteristic because the major structural proteins of the virus. The hiv-1 protease enzyme, a dimeric aspartic protease, is the enzyme liable for cleaving the gag polyprotein and consequently performs a essential position in lots of components of the hiv viral lifecycle [73,74].

Saquinavir is an inhibitor of the hiv-1 protease enzyme. Its layout is primarily based at the "peptidomimetic" precept, in which the molecule incorporates a hydroxyethylene scaffold that mimics the ordinary peptide linkage (cleaved through hiv protease) however which itself can't be cleaved. With the aid of stopping hiv-1 protease hobby, and

consequently the proteolysis of the gag polyprotein, saquinavir outcomes in the production of immature, non-infectious viral debris [73,74].

### Pharmacology

Saquinavir exerts its antiviral interest via inhibiting an enzyme essential for the hiv-1 viral lifecycle. Like other protease inhibitors, saquinavir has a propensity for participating in drug interactions – use caution whilst administering saquinavir to sufferers maintained on different pharmaceutical agents as pharmacodynamics and pharmacokinetic interactions are common. Saquinavir is understood to the qtc-c language in otherwise wholesome individuals, and must therefore be used with caution in patients maintained on different qtc-prolonging medicines or for whom prolongation of the qtc-c language may be of specific outcome (e.G. Patients with pre-current heart disease). Careful and regular tracking of affected person bloodwork is suggested, as saquinavir has been related to the development of metabolic headaches (e.G. Diabetes mellitus, hyperlipidaemia) and aggravating of pre-current liver disease [75].

### Qsar:

The correlation of structural features with the organic hobby has constantly played an important function in drug designing manner. The evaluation changed into completed on structure based calculations using numerous strategies of qsar like multiple linear regression (mlr), k-nearest neighbour (ok-nn) and partial least rectangular (pls), to set up qsar fashions for biological pastime prediction of unknown compounds. A complete of 27 peptidomimetics (saquinavir analogues) were used for the take a look at and fashions have been advanced the usage of a schooling set of twenty-two compounds and take a look at set of 5 compounds. The r2 fee of 0.959 and move demonstrated r2 (q2) of 0.926 changed into acquired while fashions have been generated using physicochemical descriptors in the course of second-qsar evaluation. In case of three-D-qsar evaluation, database alignment of all compounds was done through field healthy of steric and electrostatic molecular fields. 3-D-qsar fashions generated showed r2 of 0.81 while steric and electrostatic fields were considered as foundation of model era [76].

### G. Dexamethasone

Dexamethasone is a corticosteroid utilized in a huge range of situations for its anti-inflammatory and immunosuppressant effects. It's far used to deal with many exclusive conditions consisting of allergic disorders, pores and skin conditions, ulcerative colitis,

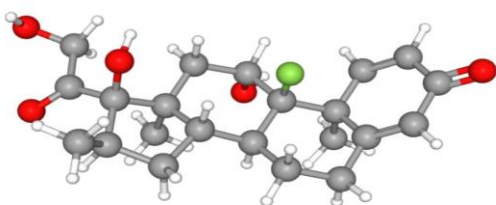
arthritis, lupus, psoriasis, or breathing disorders. It's miles the primary corticosteroid uses in sufferers with covid-19.[77]

## 2D STRUCTURE:

## IUPAC NOMENCLATURE:

1-dehydro-9 $\alpha$ -fluoro-16 $\alpha$ -methyl hydrocortisone or as 9 $\alpha$ -fluoro-11 $\beta$ ,17 $\alpha$ ,21-trihydroxy-16 $\alpha$ -methylpregna-1,4-diene-3,20-dione.

## 3D STRUCTURE:



## MOLECULAR FORMULA

C<sub>22</sub>H<sub>29</sub>FO<sub>5</sub>

## MECHANISM OF ACTION

The mechanism of action of dexamethasone depends on the dose used: the genomic (in the case of low doses) and non-genomic mechanisms (with high doses of dexamethasone). Most effects of dexamethasone are via the genomic mechanism which require a longer period, whereas dexamethasone effects through the non-genomic mechanism occur more rapidly, at the risk of more side effects [78].

*1.Genomic Mechanisms* Being small, lipophilic substances, dexamethasone can easily pass through the cell membrane by diffusion and enter the cytoplasm of the target cells and proceed by binding to glucocorticoid receptors in the cytoplasm. Dexamethasone binds to the glucocorticoid receptor

(GR) on the cell membrane, and the formation of this complex leads to translocation of the corticosteroid into the cell, where it travels to the nucleus.

*2.Non-Genomic Mechanisms* At high doses of the medication, dexamethasone binds to the membrane-associated GR on cells, such as T lymphocytes, resulting in the impairment of receptor signalling and a T lymphocyte-mediated immune response. The glucocorticoid receptor combines to integrins, leading to the activation of FAK (focal adhesion kinase). As well as that, a high dose of dexamethasone also interacts with the movement of Ca<sup>+2</sup> and Na<sup>+1</sup> across the cell membrane, resulting in a rapid reduced in the inflammation [79].

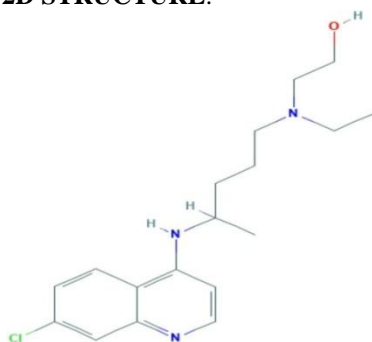
## Pharmacology

Dexamethasone is implied for bacterial infections with inflammation in acute otitis media and acute otitis externa. Intramuscular and intravenous injections are demonstrated for a number of endocrine, rheumatic, collagen, dermatologic, allergic, ophthalmic, gastrointestinal, respiratory, hematologic, neoplastic, edematous, and other conditions. Oral tablets are used for the treatment of multiple myeloma. An intravitreal implant shows some forms of macular edema and non-infectious posterior uveitis affecting the posterior of the eye. Various ophthalmic formulations are used for inflammatory conditions of the eye [80,81].

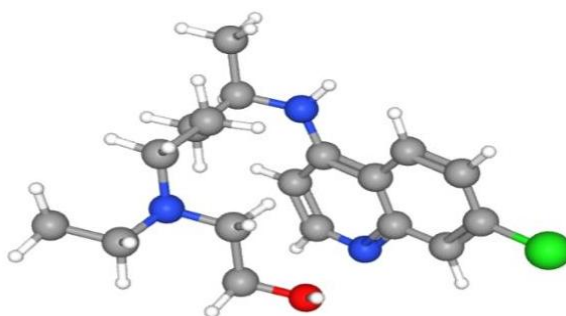
## H. HYDROXYCHLOROQUINE

Hydroxychloroquine is a drug used to prevent and treat malaria. It is also used in the treatment of certain inflammatory autoimmune diseases, including rheumatoid arthritis and a form of lupus. It is closely related to chloroquine, another antimalarial drug. It can have a number of side effects, including disruptions in heart rhythms and retinal damage. Less severe side effects include skin rash, nausea, and mood changes. It can also interact with other drugs, including antacids and insulin [82].

## 2D STRUCTURE:



## 3D STRUCTURE:



**IUPAC NOMENCLATURE:**

2-[4-[(7-chloroquinolin-4-yl)amino]pentyl-ethylamino]ethanol.

**MOLECULAR FORMULA**

C<sub>18</sub>H<sub>26</sub>ClN<sub>3</sub>O

**Mechanism of motion**

Antimalarial drugs hcq and cq have indicated advantageous results displaying a capability antiviral function towards sars-cov-2. This also has been used to have a look at numerous viral contamination inclusive of ebola, influenza and dengue. Hcq is preferred because of its higher water solubility, decrease toxicity and also viability for extended use with advanced tolerance [83,84]. hcq is more powerful & offer better treatment consequences than cq.[85] in a lab proved that, hcq has the capacity to inhibit sars-cov-2 replication in following approaches.

- this is lysosomotropic drug
- enhance ph of lysosome which have an effect on the antigen-presenting pathway and b-cellular activation
- inhibition through removal of cytokine
- hcq induces involvement in the endocytic pathway
- inhibition via barrier of sialic acid receptor
- inhibition thru regulation of ph mediated s-protein cleavage ace2 binding site

**Pharmacology**

The combination of hydroxychloroquine and azithromycin can decrease viral load in covid-19 [86] the capability of hcq is greater by way of azithromycin in lowering viral load [86] on march 23 icmr launched a announcement that recommending use of the antimalarial drug hcq as a preventive medication for folks who face a high hazard of corona virus contamination. Any other record declared that hcq was no longer capable of manipulate even moderate cases of covid-19 [87] with many mechanism of movement, they also have proven destructive effect like g.I.T. Hassle, retinopathy and qt prolongation. Hcq can also produce headache, nausea, decreasing of blood glucose, drowsiness, lower urge for food, despair, irreversible blindness, cramps and coronary heart failure. Numerous research said that, significant movement desires a large dose of the drug inside the cells and it can boom the toxicity, and an overdose can result in death.

**5. CONCLUSION**

Further have a look at claims that, hcq is slightly extra tolerable protection profile and hcq turned into stronger than cq.

**Sar:**

- nitrogen of the amine connected with the chloroquine entity is answerable for the fundamental nature of the drug.
- advent of chloro group at the 7th function of quinoline ring is highest quality for interest.
- tertiary amine on the terminal may be very crucial for the interest of the drug.
- small electron withdrawing group at seventh position of the quinoline ring is essential for the inhibition of hemozoin formation.[88]
- d-isomer of chloroquine is some what less toxic than l-isomer.

**CONSENT AND ETHICAL APPROVAL**

It is not applicable.

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

**REFERENCES**

1. Review of Computer Aided Drug Design in Drug Delivery; 2017.
2. Lengauer. Bioinformatics. From Genomes to Drugs. Wiley- VCH, Weinheim, Germany; 2002.
3. Hou T, Xu X. Recent development and Application of Virtual Screening in Drug Discovery: An Overview. Current Pharmaceutical Design. 2004;10:1011-1033.
4. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nature Reviews in Drug Discovery. 2004;3:935-949.
5. DiMasi JA, Grabowski H G. The cost of biopharmaceutical R&D: is biotech different? Managerial and Decision Economics. 2007;28:469-479.
6. Review Paper of Computer Aided Drug Designing; 2020.
7. Halloway MK. A prior Prediction of ligand affinity by energy minimization. Perspectives in Drug Discovery and Designing. 1998;9(11):63-84.



8. Bakheet TM, Doig AJ. Properties and identification of human protein drug targets. *Bioinformatics*. 2009;25:451-457.
9. Richards WG. Computer-Aided Drug Design. *Pure and Applied Chemistry*. 1994;6(68):1589-1596.
10. Walsh C. Where will new antibiotics come from? *Nat Rev Micro*. 2003;1:65–70.
11. Clark DE. What has computer-aided molecular design ever done for drug discovery? *Expert Opinion. Drug Discov*. 2006;1:103–110. DOI: 10.1517/17460441.1.2.103.
12. Huang SY, Zou X. Advances and challenges in protein-ligand docking. *Int. J. Mol. Sci*. 2010;11:3016–3034.
13. Taylor RD, Jewsbury PJ, Essex JW. A review of protein-small molecule docking methods. *J. Comput. Aided Mol. Des*. 2002;16:151–166.
14. Huang SY, Zou X. Advances and challenges in protein-ligand docking. *Int. J. Mol. Sci*. 2010;11:3016–3034
15. Jain AN. Surfex: fully automatic flexible molecular docking using a molecular similarity-based search engine. *J. Med. Chem*. 2003;46:499-511.
16. Akoka J, Comyn-Wattiau I, Laoufi N. Research on big data—A systematic mapping study. *Comput. Stand. Interfaces*. 2017;54:105–115.
17. Feher M. Consensus scoring for protein-ligand interactions. *Drug. Discov. Today*. 2006;11:421-428.
18. Shimada J, Ishchenko AV, Shakhnovich EI. Analysis of knowledge-based protein-ligand potentials using a self-consistent method. *Protein. Sci*. 2000;9:765-775.
19. Kuritzkes D, Kar S, Kirkpatrick P. Maraviroc. *Nat. Rev. Drug Discov*. 2008;7:15.
20. Bishop CM. Model-based machine learning. *Philos Trans. A Math. Phys. Eng. Sci*. 2013;371:20120222.
21. Pant S, Singh M, Ravichandiran V, Murty USN, et al. Peptide-like and small-molecule inhibitors against Covid-19. *J Biomol Struct Dyn*. 2020;1-10.
22. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62(3):932–954.
23. Lee N, Hui D, Wu A, et al. A major out break of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1986-94. DOI: 10.1056/NEJMoa030685
24. Sen GC. Viruses and interferons. *Annu Rev Microbiol*. 2001;55:255-281.
25. Tilg H. New insights into the mechanisms of interferon Alfa: An immunoregulator and anti-inflammatory cytokine. *Gastroenterology*. 1997;112:1017-1021.
26. Morgenstern B, Michaelis M, Baer PC, Doerr HW, Cinatt J. Ribavirin and interferon-beta synergistically inhibits SARS-associated corona virus replication in animal and human cell lines. *Biochem Biophys Res Commun*. 2005;326:905-8. DOI: 10.1016/j.bbrc.2004.11.128
27. Wang WK, Chen SY, Liu IJ, Kao CL, Chen HL, Chiang BL, et al. Temporal relationship of viral load, ribavirin, interleukin (IL)-6, IL-8, and clinical progression in patients with severe acute respiratory syndrome. *Clin Infect Dis*. 2004;39:1071-5. DOI: 10.1086/423808
28. Khalid M, Al Rabiah F, Khan B, Al Mobeireek A, Butt TS, Al Mutairy E. Ribavirin and interferon- $\alpha$ 2b as primary and preventive treatment for Middle East respiratory syndrome corona virus: a preliminary report of two cases *Antivir Ther*. 2005;20:87-91. DOI: 10.3851/IMP2792
29. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life sci*. 2020;248:117477. DOI: 10.1016/j.lfs.2020.117477
30. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019. (COVID-19). *Drug Discov Ther*. 2020;14:58-60. DOI: 10.5582/ddt.2020.01012
31. Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. *Life Sci*. 2020;253:117592. DOI: 10.1016/j.lfs.2020.117592
32. Cameron CE, Castro C. The mechanism of action of ribavirin: lethal mutagenesis of RNA virus genomes mediated by the viral RNA-dependent RNA polymerase. *Curr Opin Infect Dis*. 2001;14:757-64.
33. Tsang KW, Ho PL, Ooi GC, Yee WK, Wang T, Chan-Yeung M, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong [online]. *N Engl J Med*. Available: [content.nejm.org/cgi/reprint/NEJMoa030666v3](http://content.nejm.org/cgi/reprint/NEJMoa030666v3) (posted 2003 Mar 31; accessed 2003 Apr-15).
34. Pharmaceuticals and Medical Devices Agency: Avigan (favipiravir) Review Report.
35. Jin Z, Smith LK, Rajwanshi VK, Kim B, Deval J. The ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5'-triphosphate towards influenza A virus polymerase. *PLoS One*. 2013;8.

36. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys Biol Sci.* 2017;93(7):449-463. DOI: 10.2183/pjab.93.027
37. Baranovich et. al.; 2013.
38. Baranovich T, Wong SS, Armstrong J. 705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro. *J Virol.* 2013;87:3741-3751.
39. Rhyman L, Tursun M, Abdallah HH, Choong YS, Parlak C, Kharkar P, Ramasami P. Theoretical investigation of the derivatives of favipiravir (T-705) as potential drugs for Ebola virus. *Physical Sciences Reviews.* 2018;3(9).
40. Zhong H, Wang Y, Zhang ZL, Liu YX, Le KJ, Cui M, Yu YT, Gu ZC, Gao Y, Lin HW. Efficacy and safety of current therapeutic options for COVID-19- lessons to be learnt from SARS and MERS epidemics: A systematic review and meta-analysis. *Pharmacol. Res.* 2020;157:104872. DOI: 10.1016/j.phrs.2020.104872
41. Dagens A, Sigfrid L, Cae E, et al. Scope, quality, and inclusivity of clinical guidelines produced early in the COVID-19 pandemic: rapid review. *BMJ.* 2020;369:m1936
42. Nukoolkarn V, Lee VS, Malaisree M, Aruksakulwong O, Hannongbua S. Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. *J Theor Biol.* 2008;256:861-867.
43. Chen F, Chan KH, Jiang Y, et al. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol.* 2004;31:69-75.
44. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East Respiratory Syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother.* 2014;58:4875-4884.
45. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun.* 2020;11:222.
46. Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. *Science*; 2020. DOI: 10.1126/science.abb3405
47. Anand K, Ziebuhr J, Wadhvani P, et al. Corona virus main proteinase (3CL pro) structure: basis for design of anti-SARS drugs. *Science.* 2003;300(5626):1763-7. DOI: 10.1126/science
48. Vastag B. Old drugs for a new bug. *JAMA.* 2003;290(13):1695-96.
49. Choy KT, Yin-Lam Wong A, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res.* 2020:104786. DOI: 10.1016/j.antiviral.2020.104786
50. Takashiro E, Hayakawa I, Nitta T, Kasuya A, Miyamoto S, Ozawa Y, Yagi R, Yamamoto I, Shibayama T, Nakagawa A, Yabe Y. Structure-activity relationship of HIV-1 protease inhibitors containing  $\alpha$ -hydroxy- $\beta$ -amino acids. Detailed study of P1 site. *Bioorganic & medicinal chemistry.* 1999;7(9):2063-72.
51. Computed by LexiChem 2.6.6 (PubChem release 2019.06.18).
52. Malin JJ, Suarez I, Priesner V, Fatkenheuer G, Rybniker J. Remdesivir against COVID-19 and Other Viral Diseases. *Clin Microbiol Rev.* 2020;34(1). Pii: 34/1/e00162-20. DOI: 10.1128/CMR.00162-20.
53. Humeniuk R, Mathias A, Kirby BJ, Lutz JD, Cao H, Osinusi A, Babusis D, Porter D, Wei X, Ling J, Reddy YS, German P. Pharmacokinetic, Pharmacodynamics, and Drug-Interaction Profile of Remdesivir, a SARS-CoV-2 Replication Inhibitor. *Clinical pharmacokinetics*; 2021.
54. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, Gotte M. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem.* 2020;295(20):6785-6797. DOI: 10.1074/jbc.RA120.013679. Epub 2020 Apr 13.
55. De Clercq E. Strategies in the design of antiviral drugs. *Nat Rev Drug Discov.* 2002;1(1):13-25. DOI: 10.1038/nrd703. Mehellou Y, Balzarini J, McGuigan C. Aryloxy phosphoramidate triesters: a technology for delivering monophosphorylated nucleosides and sugars into cells. *Chem Med Chem.* 2009;4(11):1779-1791. DOI: 10.1002/cmdc.200900289
56. Seley-Radtke KL, Yates MK. The evolution of nucleoside analogue antivirals: a review for chemists and non-chemists. Part 1: Early structural modifications to the nucleoside scaffold. *Antiviral Res.* 2018; 154:66-86. DOI: 10.1016/j.antiviral.2018.04.004
57. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir

- and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun.* 2020;11(1):1–4.  
DOI: 10.1038/s41467-019-13940-6
58. WHO model list of essential medicines. Accessed March 29,2011.
  59. Elfiky AA. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, And Tenofovir against SARS-CoV-2 RdRp: A molecular docking study. *Life Sci.* 2020;253:117592.
  60. Chien M, AndersonTK, Jockusch S, et al. Nucleotide analogues as inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target for COVID-19. *J Proteomase Res.* 2020;19:4690-7.
  61. Zandi K, Amblard F, Musall K, et al. Repurposing nucleoside analogs for human corona viruses. *Antimicrob Agents Chemother.* 2020;65.  
DOI: 10.1128/AAC.01652-20.
  62. Muralidharan N, Sakthivel R, Velmurugan D, Gromiha MM. Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19. *J Biomol Struct Dyn.* 2020;1-6.  
DOI: 10.1080/07391102.2020.1752802.
  63. Anderson PL, Kiser JJ, Gardner EM, Rower JE, Meditz A, Grant RM. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *J Antimicrob Chemother.* 2011;66(2):240-50.
  64. Chien M, Anderson TK, Jockusch S, et al. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. *J Proteome Res.* 2020;19(11):4690-4697.
  65. Elfiky AA. Ribavirin, remdesivir , sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. *Life Sci.* 2020;253:117592.
  66. Clososki GC, Soldi RA, Silva RM da, et al. Tenofovir Disoproxil Fumarate: New chemical developments and encouraging in vitro biological results for SARS-CoV-2. *J Braz Chem Soc.* 2020;31:1552-6.
  67. Park S-J, Yu K-M, Kim T-I, et al. Antiviral Efficacies of FDA- approved drugs against SARS-CoV-2 infection in Ferrets. *mBio.* 2020;11.  
DOI:10.1128/mBio.01114-20.
  68. Del Amo J, Polo R, Moreno S, et al. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: a cohort study. *Ann Intern Med.* 2020;173(7): 536-541.
  69. Elfiky A. A. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sci.* 2020;253:117592.
  70. Clososki GC, Soldi RA, RMD Silva, et al. Tenofovir disoproxil fumarate: new chemical developments and encouraging in vitro biological results for SARS-CoV-2. *J Braz Chem Soc.* 2020;31(8):1552-1556.
  71. Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. AIDS Clinical Trials Group. Collier AC, Coombs RW, Schoenfeld DA, Bassett RL, Timpone J, Baruch A, Jones M, Facey K, Whitacre C, McAuliffe VJ, Friedman HM, Merigan TC, Reichman RC, Hooper C, Corey LN *Engl J Med.* 1996;16:1011-1017.  
MED:8598838
  72. Schapiro JM, et al. The effect of high-dose saquinavir on viral load and CD4+ T-cell counts in HIV-infected patients. *Ann Intern Med.* 1996;124(12):1039–1050.
  73. De Clercq E. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. *Int J Antimicrob Agents.* 2009;33(4):307-20.  
DOI: 10.1016/j.ijantimicag.2008.10.010. Epub 2008 Dec 23.
  74. DA Approved Drug Products: Invirase (saquinavir mesylate) oral tablets.
  75. LiverTox LICENSE  
<https://www.nlm.nih.gov/copyright.html>  
Saquinavir
  76. South Asian Journal of Experimental Biology, Vol 2, No 3 (2012). QSAR of Saquinavir Analogues (Peptidomimetics) as Potent HIV-Protease Inhibitors. Vandana Saini, Ajit Kumar.
  77. Available:<https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-dexamethasone>.
  78. Chikanza IC. Mechanisms of corticosteroid resistance in rheumatoid arthritis: a putative role for the corticosteroid receptor beta isoform. *Ann N Y Acad Sci.* 2002;966:39–48.  
DOI: 10.1111/j.1749-6632.2002.tb04200.x.
  79. Grzanka A, Misiołek M, Golusiński W, Jarzab J. Molecular mechanisms of glucocorticoids action: implications for treatment of rhinosinusitis and nasal polyposis. *Eur Arch Otorhinolaryngol.* 2011;268:247–253.  
DOI: 10.1007/s00405-010-1330-z.
  80. FDA Approved Drug Products: Maxitrol Neomycin, Polymyxin B, and Dexamethasone Ophthalmic Ointment.

81. FDA Approved Drug Products: Tobradex Tobramycin and Dexamethasone Ophthalmic Suspension.
82. Available:<https://www.dictionary.com/browse/hydroxychloroquine> DICTIONARY.COM UNABRIDGED BASED ON THE RANDOM HOUSE UNABRIDGED DICTIONARY, © RANDOM HOUSE, INC. 2021
83. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents.* 2020;55:19–20. DOI: 10.1016/j.ijantimicag.2020.105938.
84. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): Chloroquine or hydroxychloroquine. *Int J Antimicrob Agents.* 2020;55:1–3. DOI: 10.1016/j.ijantimicag.2020.105945.
85. Gevers S, Kwa MSG, Wijnans E, van Nieuwkoop C. Safety considerations for chloroquine and hydroxychloroquine in the treatment of COVID-19. *Clin Microbiol Infect* Published online. 2020:4539–47. DOI: 10.1016/j.cmi.2020.05.006.
86. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* 2020;105949. Available:10.1016/j.ijantimicag.2020.105949C  
clinical trial favouring use of HCQ with azithromycin in COVID-19 patients.
87. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. *Ann Intern Med.* 2020:M20–4207. DOI: 10.7326/M20-4207  
Accessed 22 July 2020.
88. Muraleedharan KM, Avery MA. In *Comprehensive Medicinal Chemistry II. Therapeutic Areas II: Cancer, Infectious Diseases, Inflammation, Immunology and Dermatology*; Taylor JB, Triggler DJ, Eds.