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Pharmaceutical Sciences **REVIEW ARTICLE ……!!!**

"A REVIEW ON CURRENT APPROACHES OF DEVELOPMENT OF ANTIVIRAL DRUGS"

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KEYWORDS:

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ABSTRACT

For hundreds of years, people were trying to find safe ways of the treatment of viral infections. But this was found to be very difficult due to the ability of viruses to use the host-cell to replicate, so the drugs may cause harm also to host cells. Nevertheless, today some methods are used to treat or minimize the symptoms caused by the viral infection. According to the mechanism of action old and newly produced drugs are classified in three basic classes that is Inhibition of the entrance to the host cell, Inhibition of specific viral enzymes, such as reverse transcriptase, that is used by viruses to generate DNA from RNA, and RNA polymerase, that does not exist in the host cell, Inhibition of viral proteins production, such as in the case of HIV virus.In this review, we discussed on newly developed drugs for the most important diseases like herpetic infection, HIV and Hepatitis C caused by responsible viruses, and the older drugs that have been used until today will be mentioned only briefly.

INTRODUCTION:

Viruses are non-cellular forms of life composed of proteins and a nucleic acid, which is enclosed in a protective capsid. The first virus that was described was tobacco mosaic virus in 1892 by Dmitri Ivanovsky. Since then, about 5.000 viruses have been discovered and many ways of the treatment of viral infection. [1] Viruses have many differences that characterize them from microorganisms: they contain only one type of nucleic acid (DNA or RNA), but never both simultaneously and, they do not have ribosomes or other cellular organelles. (Table 1) This is the reason why all viruses demand a host cell to multiply and outside of it they are inactive. [2]

Table no. 1-types of viruses depending on nucleic acid structure

Viruses with double-stranded DNA	Adenovirus, herpes virus, poxvirus, vaccinia virus
Viruses with single-stranded DNA	some bacteriophages
Viruses with double-stranded RNA	Retrovirus
Viruses with single-stranded RNA	Poliovirus, influenza virus, HIV, RNA oncogenic

Each virus affects only some cells (*e.g.* the HIV virus affects CD4+ T cells and macrophages). The multiplication cycle of viruses consists of four main parts. First is the entrance of the virus into the host-cell. Immediately after, the expression of virus's genes, the multiplication of the nucleic acid and the synthesis of proteins follows. New virions are formed and released from the host-cell by cell lysis. [3]Since 1960's many antiviral drugs have been discovered and gave us the opportunity to deal with many viral infections that we could not before. Most of them are efficiently used nowadays, while new substances are tested to produce new, safer and more efficient drugs.[3]

Herpetic infections

Herpetic infections are very common among human population and sometimes can lead to serious diseases, such as cancer. The cycle of herpes virus is characterized by activation and remission periods.[8] In the active period, virus-containing blisters occur and this situation can last several days, or sometimes, up to three weeks. In that period, the virus becomes contagious

and other people can be easily contaminated by direct skin contact or body fluids. On the other hand, in the remission period the virus stays in the sensory nerves of the central nervous system (CNS) without causing symptoms of infection (asymptomatic period).[4]

Drugs used for all types of herpetic infections

A. **Acyclic Nucleosides**:

The identification of acyclovir as a selective inhibitor of herpes simplex virus (HSV) replication was an important breakthrough in the development of antiviral drugs. Its selectivity is based on a specific recognition by the HSV-encoded thymidine kinase. Gradually, the derivatives of acyclovir with improved properties have been developed. [11]. Ganciclovir is effective also against CMV infections.[12]Valaciclovir and valganciclovir are prodrugs that are in vivo converted to the parent drug. Penciclovir is the active metabolite of the oral product famciclovir. (Figure No 1).Acyclovir is converted to acyclovir triphosphate by enzyme thymidine kinase and then it is incorporated into the viral DNA.

Table No.2 Classification of herpes virus

Types of Herpes virus	Causes
Herpes simplex type 1 (HSV-1) and type 2 (HSV-2)	oral and genital herpes
Epstein-Barr virus	infectious mononucleosis
Varicella-Zoster virus	Chickenpox(children), herpes zoster(adults)
Human Cytomegalovirus	Immunocomppressant

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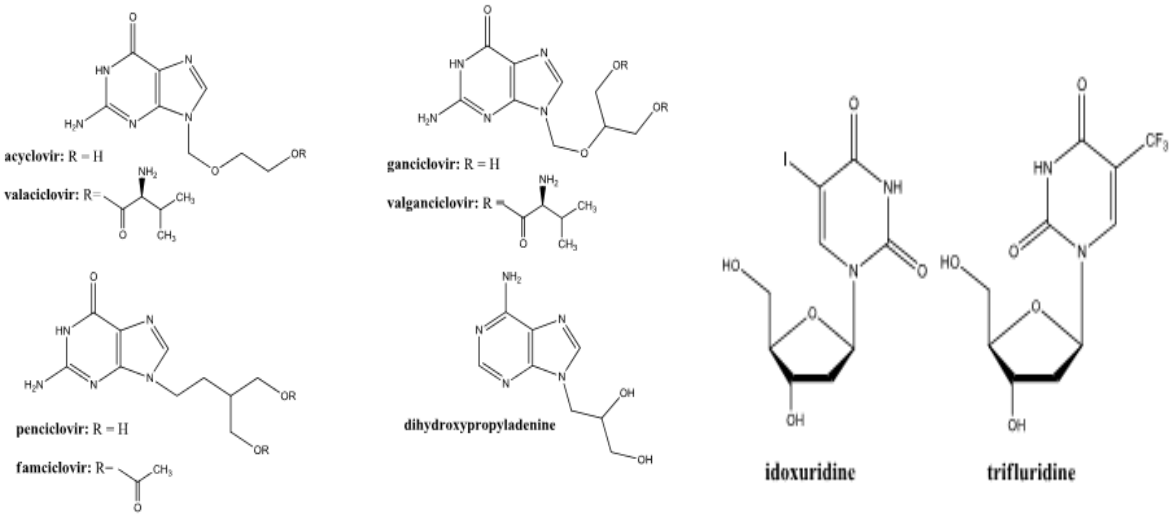


Figure No 1. A. Acyclic Nucleosides AnalogousB. Nucleoside analogues

B. Nucleoside analogues -Idoxuridine is a nucleoside analogue used only topically for treatment of herpes simplex keratitis. Trifluridine is used topically in the eye for treatment of herpetic infections.[4]

C. Inosine pranobex -It is a complex of inosine with dimepranol acedoben – (±)-1-(dimethylamino)propan-2-ol *p*-acetamidobenzoate). It has been used in the treatment of subacute sclerosing panencephalitis and herpes simplex infections.[5]

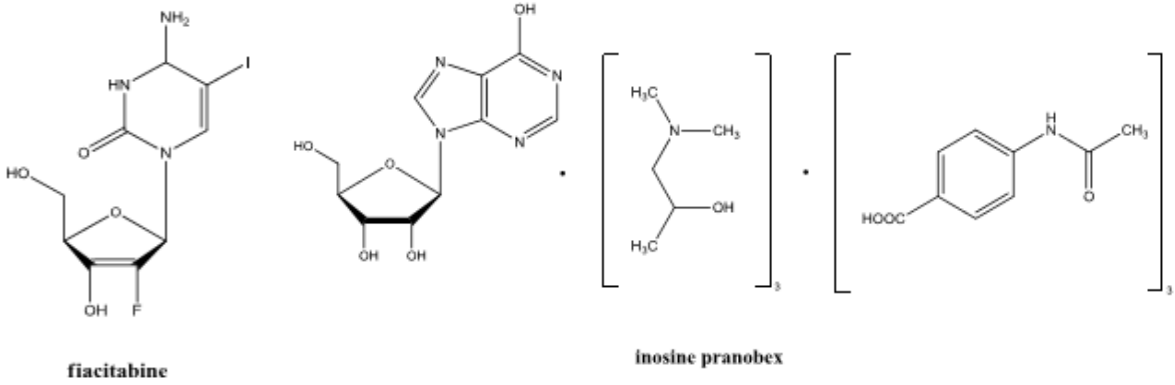


Figure no 2. Drugs used in Epstein-Barr virus

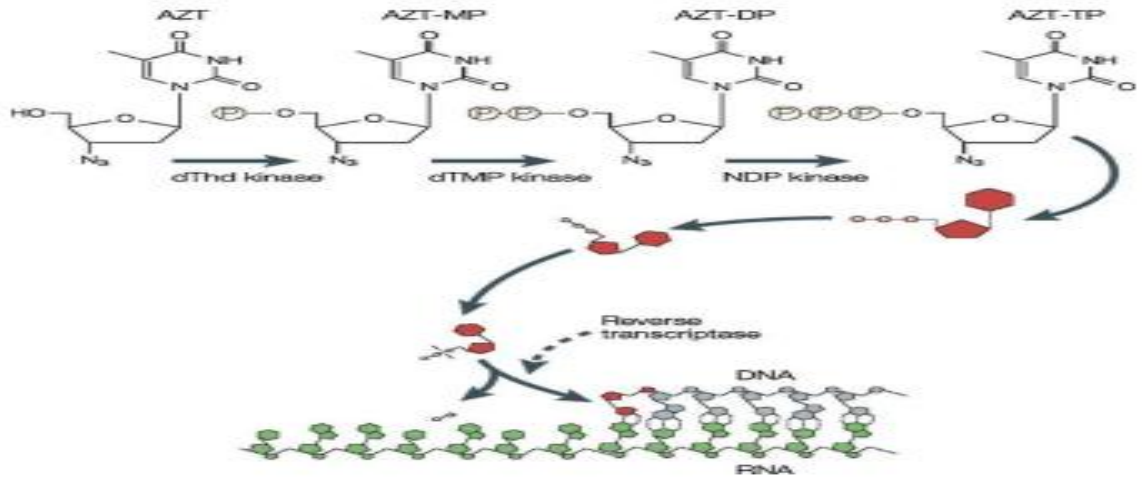
HIV infections

HIV (Human Immunodeficiency Virus) tends to be a modern plague. It infects T helper cells (CD4+ T cells) and macrophages, important immune system cells. This leads to a failure in the patient's immune system, which cannot deal even with the simplest infections. People infected with HIV virus usually suffer from Pneumocystis pneumonia and CMV keratitis. There are recognized two types of HIV virus, HIV-1, which causes more serious effects and HIV-2 with low transmission ability. The virus's genome is single-stranded RNA and that is the reason that the enzyme reverse transcriptase, which converts RNA into DNA, is needed. The HIV has high mutation ability, so vaccination is ineffective at this situation. The virus is mainly transmitted via blood, breast milk and semen.[6]

Drugs used for HIV infections

Nucleoside inhibitors of reverse transcriptase

Didanosine is a dideoxynucleoside, reverse transcriptase inhibitor and it is combined with other antiretroviral agents, such as stavudine, for the treatment of HIV patients. Its mechanism of action is an early termination of the viral genetic material synthesis. Zidovudine is used in post-exposure prophylaxis together with lamivudine.Zalcitabine is a pyrimidine analogue and is less potent than the other drugs of this group. Similarly, emtricitabine (a pyrimidine antimetabolite) abacavir (a guanosine analogue) are always used in combination with other antiretroviral agents.



Mechanism of action of zidovudine (AZT). Following phosphorylation to its triphosphate form

(AZT-TP), AZT acts as a competitive inhibitor/alternative substrate with respect to dTTP in the reverse transcriptase reaction

Development of New Antivirals

Developing new antiviral drugs is difficult especially because the new agents must subject in certain regulations. They must be effective to one or more kinds of diseases, safe enough to limit undesirable effects and to pass qualitative analysis. Discovery of new active substances is rare. Generally, a prototype structure (lead) is discovered. This substance has many undesirable characteristics, such as low absorption capacity or many side effects. That is the reason that new drug structures are developed by the improvement of already existing pharmacological substances, *e.g.* by adding a group into the basic skeleton of the compound to improve lipophilicity, absorption and duration of the action and to avoid some serious adverse effects. For a drug to be approved for registering it must pass preclinical and clinical trials. Preclinical trials include animal testing of the active substance of the drug to obtain information about pharmacokinetic and pharmacodynamic characteristics and its physicochemical properties. On the other hand, clinical evaluation is composed of four stages (phases):

Phase 1: it is performed on healthy volunteers to obtain information about the safety and tolerance of the drugs

Phase 2: it is performed on a small number of patients, to find out the optimal dosage of the drug

Phase 3: a larger number of patients is used. At the end of this phase the drug producer submits the new drug application (NDA), which shown the safety and efficacy of the drug

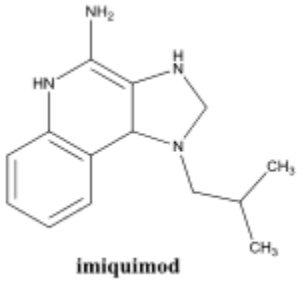
Phase 4: research on the drug after its approval. The medicine treated patients record all the possible side effects

New drugs development for herpetic infections

Although already approved drugs for the treatment of herpes simplex and are highly effective, there is a need for newly developed substances for the treatment of resistant viruses and for the prevention of viral reactivation.

TLR agonists

Toll-like receptors are proteins that are found in immune system cells, like macrophages and dendritic cells, and help them to recognize special microbe-derived molecules. As a result, they enhance the immunity of the organism against infections. There are several types of toll-like receptors located mainly in the cell surface (TLR-1– TLR-13). Several experiments have shown that TLR (toll-like receptor) agonists lead to the stimulation of the immune response. It was shown that mice treated with polycytidylic acid, which is a TLR-3 agonist, survived for sufficiently longer time than with TLR-4 or TLR-5 agonists.Imiquimodis a topical TLR7/8 agonist that has been given as a treatment of rare skin cancers, such as malignant melanomas, but has also shown positive results in the reduction of the warts caused by HSV-2 virus when applied twice a week. It is a relatively old drug which nowadays undergoes further clinical studies to be approved for the treatment of herpetic infections.[7]



imiquimod

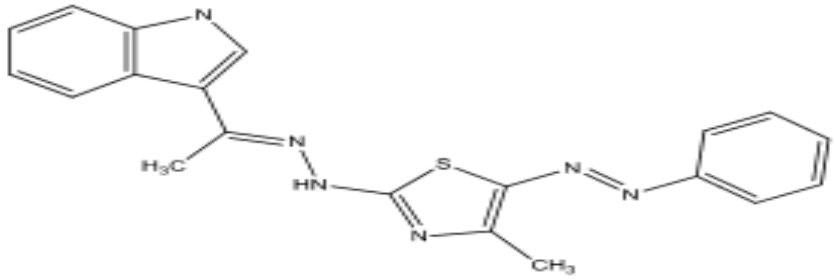
Helicase/primase inhibitors

Helicase is an enzyme with the function to unroll the genetic material (DNA or RNA) and plays an important role in replication, transcription and translation. Primase is also an enzyme that converts sRNA to ssDNA and has primary importance to DNA replication. This category of drugs is under experimental methods with not known clinical experience. The candidate drug BAY 57-1293 was found to be more effective than acyclovir in the treatment of genital and ocular herpes infection in laboratory animals.

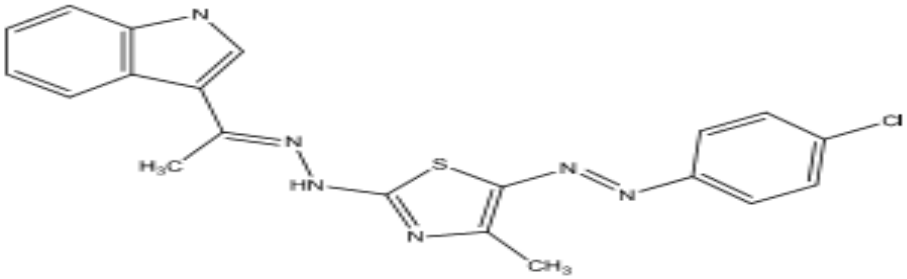
Indole-based heterocycles

It is known that indole has many pharmacological properties including anti-inflammatory, antidepressant, antiproliferative and antiherpetic by inhibiting HSV-1intergrase. The goal now is to synthesize new indole derivatives with improved antiviral activity. Several experiments in

animals have shown that some indole-containing compounds *e.g.* 2-{2-[1-(1*H*-indol-3-yl)ethylidene]hydrazinyl}-4-methyl-5-(phenyldiazeny)thiazole and 2-{2-[1-(1*H*-indol-3-yl)ethylidene]hydrazinyl}-5-[(4-chlorophenyl)diazenyl]-4-methylthiazole have shown positive results in reducing of the plaques of Herpes simplex type 1 (HSV-1).



2-{2-[1-(1H-indol-3-yl)ethylidene]hydrazinyl}-4-methyl-5-(phenyldiazeny)thiazole



2-{2-[1-(1*H*-indol-3-yl)ethylidene]hydrazinyl}-5-[(4-chlorophenyl)diazenyl]-4-methylthiazole

Anti-heparan sulfate peptides

The molecule of heparin sulfate (HS) and one modification form of it, 3-*O*-sulfated heparan sulfate (3-OS HS) work as attachment site for HSV-1 virus. 3-*O*-sulfated heparan sulfate is produced enzymatically from HS by 3-*O*-sulfortransferases and works as a mediator of the penetration of HSV-1 virus into the cells. Two different anti-HS peptides were tested against HSV-1, G1 peptide (LRSRTKIIRIRH) and G2 peptide (MPRRRRIRRRQK). Both successfully blocked the entry of the virus into thecell and with further future experiments it will be determined if anti-HS peptides could be used as a first-line treatment against HSV-1.

Varicella zoster

Salivary micro-RNAs

MicroRNAs (miRNAs) are non-coding RNA type that bind and suppress complementary mRNA targets. In our case, the target is m-RNA of VZV. These mi-RNAs are found in the salivary microvesicles of humans and could be used as effective antiviral agents against ophthalmic herpes zoster caused by Varicella-zoster virus (VZV). Microvesicles contain about 20 mi-RNAs, which can inhibit the VZV's mRNAs and, as a result, the inhibition of their translation and replication. As a mechanism of action, it is suggested that human salivary mi-RNAs are bound to plasma proteins and enter the corneal cells of the eye via endocytosis.

Human Cytomegalovirus

Peptides targeting glycoprotein b (gb)

Glycoprotein b is a glycoprotein found on the outer layer of the envelope of herpes viruses. It works as a "fusion protein" and it is required for the entry of the virus into the cells. Due to the increased need for better anti-HCMV drugs with decreased side effects and cytotoxicity, therapeutic peptides which target glycoprotein g5 of human cytomegalovirus were developed as potent antivirals. It was found that gb contains numerous regions, which can interact with lipid bilayers and hydrophobic surfaces of the proteins. Several peptides at many concentrations were incubated with human fibroblastic cells and afterwards the cells were infected with HCMV. The results were positive and exhibit inhibition of HCMV infection with a range between 60% – 97%, depending on the type of the used peptide. As a result, gb inhibition peptides could be a basis for new therapeutics for the prevention of Human cytomegalovirus infection[8]

HIV infections

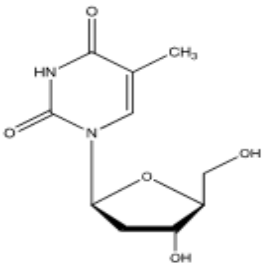
Treatment of Human Immunodeficiency virus is difficult and complex, due to the ability of the HIV virus to mutate. Modern therapeutic pattern is HAART (Highly Active Antiretroviral Therapy), in which combinations of three or even more antiviral agents are used (usually combination of non-nucleoside reverse transcriptase inhibitors, HIV protease inhibitors and nucleoside reverse transcriptase inhibitors). HAART has succeeded in the decrease of the amount of virus present in blood and in the increase in life expectancy.

Nucleoside reverse transcriptase inhibitors

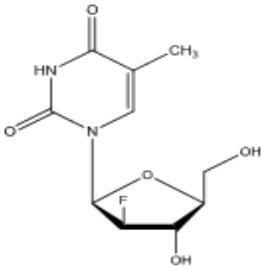
Telbivudine, clevudine and entecavir belong to nucleoside reverse transcriptase inhibitors and are registered as antiviral drug against chronic hepatitis B. They are also active in a high range of retroviruses, such as HIV. A recent research demonstrated that could be also used in HIV-1/HBV co-infection. In a recent treatment of a patient positive in HIV and hepatitis B, both treated with adefovir dipivoxyl and telbivudine, it was found that when administration of telbivudine discontinued the viral load of HIV was significantly increased. When it was administered again after a two-week interval, the viral load was decreased. This situation could be a major step for future approval of telbivudine as an anti-HIV-1 agent.Clevudine is a unique antiviral nucleotide analogue because its antiviral activity persists after discontinuation of therapy, as demonstrated by in vitro and in vivo trials was recently approved for HBV infected patients infected with HIV. Unfortunately, it can induce myopathy.Similarly, entecavir is used for the treatment of chronic hepatitis B and it is also approved for chronic hepatitis C and HIV co-infection. In entecavir, the sugar moiety is replaced with an oxygen non-containing five membered ring[9].

Non-nucleoside reverse transcriptase inhibitors

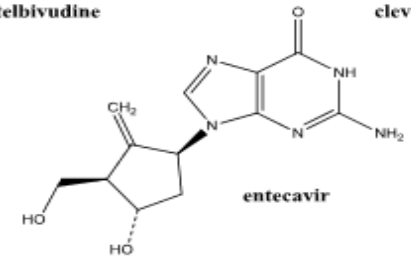
Etravirine belongs to the second generation of non-nucleoside reverse transcriptase inhibitors and it is indicated for the treatment of HIV-1. It is a diarylpyrimidine molecule that inhibits the enzyme reverse transcriptase in a non-competitive manner and leads to the increased amount of CD4+ T cells. Its advantage is that etravirine is active even against specific viral mutation, in which efavirenz and nevirapine are not active.



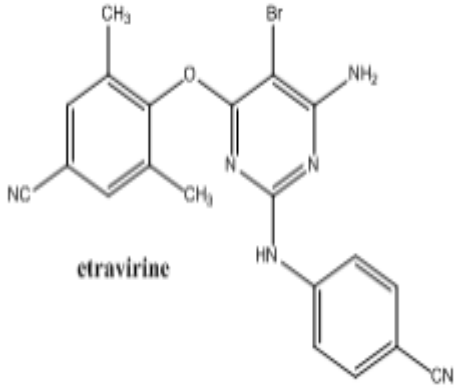
telbivudine



clevudine



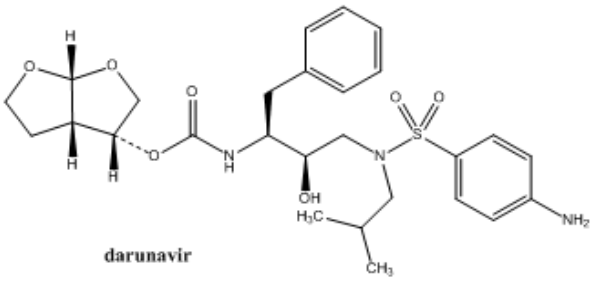
entecavir



etravirine

HIV protease inhibitors

Darunavir is an oral second generation HIV protease inhibitor used in antiretroviral therapy (ART). It is generally quite tolerated from patients and exhibits fewer side effects than older antivirals of the same class, like indinavir. It is very usefull in the treatment of HIV-resistant patients.

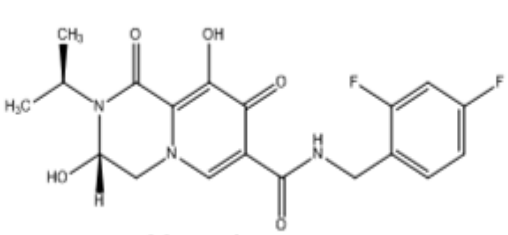


darunavir

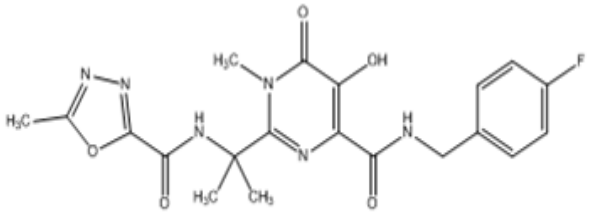
HIV integrase inhibitors

Dolutegravir is a HIV-integrase inhibitor, a new class of anti-HIV drugs. Like all drugs of this category, it works by inhibiting viral enzyme integrase, which is responsible for the integration of the viral RNA into the chromosomes of the infected cells. In randomized control trials, it exhibited higher efficacy than raltegravir and efavirenz and did not showed any serious side effects. Dolutegravir could be administered once daily, without any pharmacological booster like

ritonavir and can be combined with other antiviral agents, *e.g.* abacavir and lamivudine to increase efficacy against HIV.Raltegravir is the first integrase inhibitor approved. It was recentlyreceived approval for children aged 2-18 and it is available in chewable form. Unlike dolutegravir, it is administered twice a day and we can use it as monotherapy or in combination with other antiviral agents against HIV.[10]



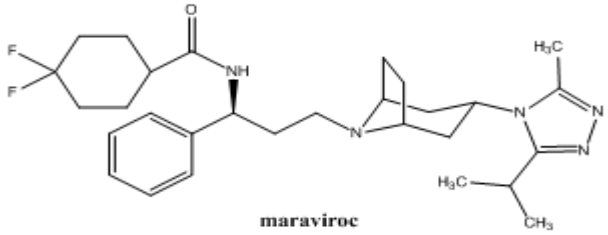
dolutegravir



raltegravir

chemokine receptor type 5 antagonists

Maraviroc is an CCR5 (C-chemokine receptor type 5) antagonist and the only agent of this class that has been approved for the treatment of HIV infection and AIDS in adult patients with exclusively CCR5-tropic infection. CCR5 is a protein found on the white blood cells, which HIV virus uses to enter and infect the immune system cells. In placebo controlled studies, maraviroc seemed to be very effective and simultaneously safe enough with few side effects, but can lead to virologic failure and rebound HIV-1 viraemia.[11]



maraviroc

Other drugs

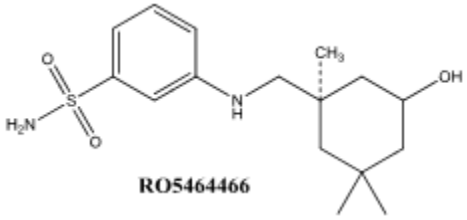
Scorpion venom peptide derivative Kn2-7 was designed based on BmKn2 peptide, to increase lipophilicity. After many trials and screening assays it was found that this peptide selectively inhibits HIV-1 and interacts in a direct way with the virus. It was also able to inhibit CXCR4-

tropic replication of HIV-1 virus and with further investigation could be formed as a major antiviral agent against HIV-1

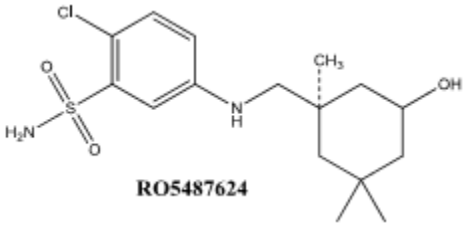
New drugs for influenza infections

Benzenesulfonamide Derivatives Targeting Viral Hemagglutinin

Hemagglutinin (HA) is a glycoprotein present in the surface of influenza A virus. It "recognizes" sialic acid on the cell membranes and allows the fusion of the viral membrane with the host cell membrane. There are several types of hemagglutinin, but only H1, H2 and H3 are present in human influenza viruses. As far as it concerns antiviral activity of benzenesulfonamide derivatives, recent pharmacokinetic studies shown that substances RO5464466 and RO5487624 lead to successful inhibition of Influenza A virus. Their efficacy was also tested *in vivo* and both were very active against H1N1 strain. RO5487624 possesses better pharmacokinetic properties and better *in vitro* activity against Influenza virus[12]



RO5464466

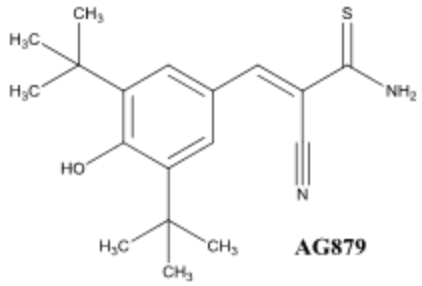


RO5487624

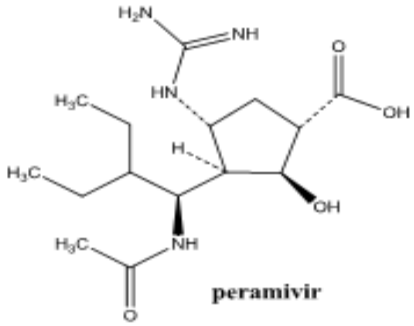
Receptor Tyrosine Kinase Inhibitors

Tyrosine kinase is an enzyme that involves in the phosphorylation of many proteins and takes part in the activation of signal transduction cascades. Drugs that use this mechanism usually are used as potent anticancer agents. However, recent studies assure that some newly developed compound could possess antiviral activities.

Substance AG879 – (*E*)-2-cyano-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)prop-2-enethioamide – a tyrphostin-class RTKI, is under clinical trials and has shown inhibitory activity in the replication of many viruses including Influenza A and Herpes simplex. Its activity is tested both *in vivo* and *in vitro* and it showed low resistance (unlike amantadine), high selectivity and large spectrum of activity(against influenza A and B).



AG879



peramivir

Neuraminidase inhibitors

Peramivir is a neuraminidase inhibitor that it is under clinical trials but has already been used in intravenous form for the treatment of H1N1 infection when the patients were unsuccessfully treated with other drugs, like oseltamivir. In recent clinical trials, patients who treated with peramivir present higher probability of been infected with 35 pneumonias. When the trials will be completed, it will be shown if peramivir deserves to be used in clinical practice. [13]

New drugs for Hepatitis C

Hepatitis C virus proteases inhibitors

This class of agents is also known as direct-acting antiviral drugs (DAA). Until now, there are two drugs that have been approved, boceprevir and telaprevir. They both work by inhibition of NS3/4A protease, which is necessary for viral replication and are combined with pegylated interferon 2α and ribavirin. In randomized controlled trials, the drugs proved to be very effective against HCV and quite safe without serious side effectsOther drugs of this class are under development.

Daclastavir is the most potent NS5A inhibitor and showed a very good therapeutic index *in vitro*. It is very effectively distributed into the liver and it is available in oral dosage form. Similarly, danoprevir, vaniprevir and asunaprevir nowadays undergo clinical trials, in which it was found that they have a good therapeutic index and successfully inhibit replication of HCV virus. Asunaprevir, is a serine protease (NS3) inhibitor and its combinations with ribavirin and pegylated interferon 2α are tested.[13]

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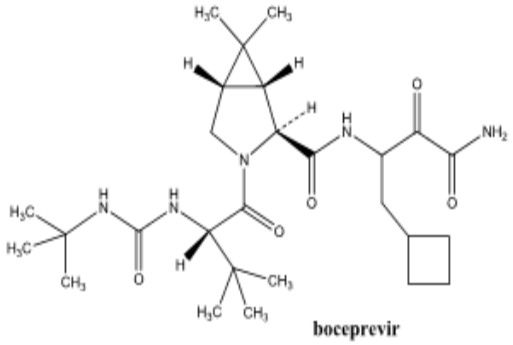
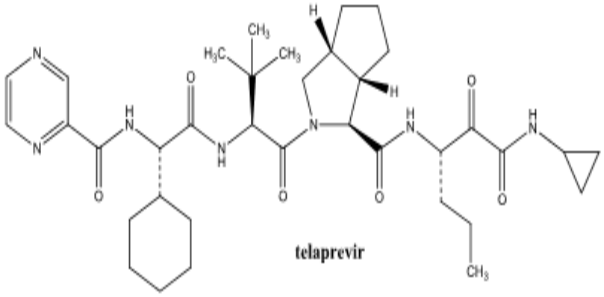
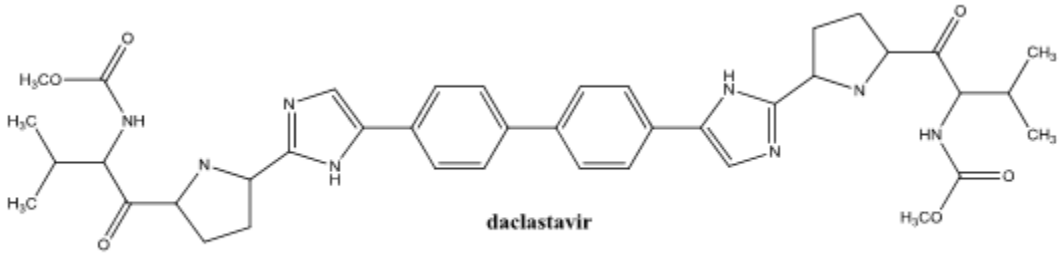


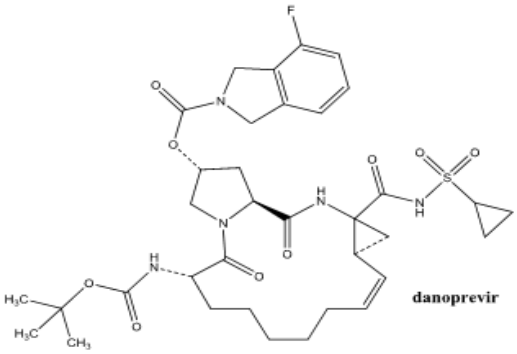
boceprevir



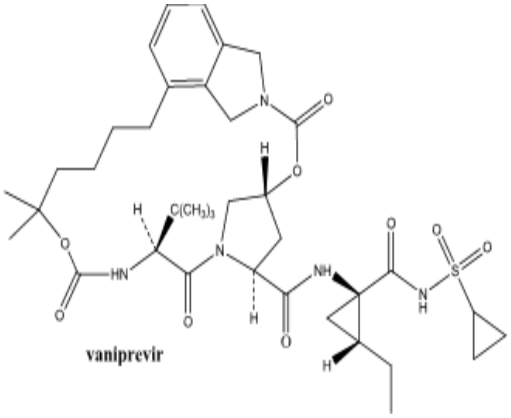
telaprevir



daclastavir



danoprevir



vaniprevir

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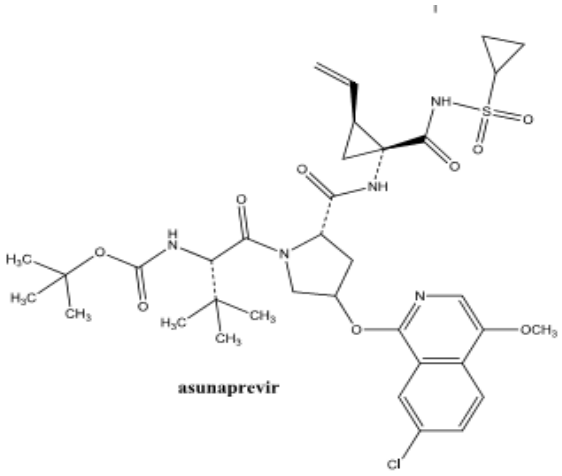
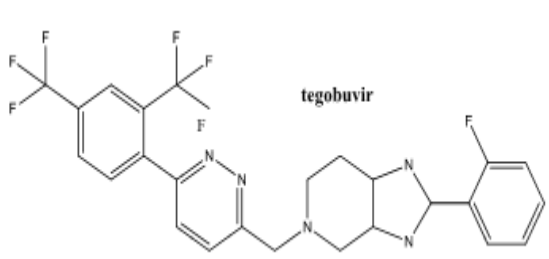
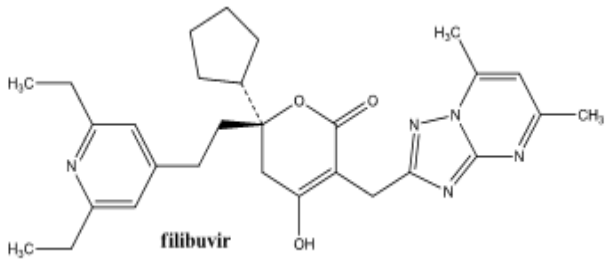


NS5B polymerase inhibitors

NS5B is an RNA polymerase and its primary role is in the replication of the viral genome. Inhibition of this enzyme is the target of new drugs concerning the treatment of chronic hepatitis C which is classified in to Non-nucleoside type(tegobuvir, filibuvir, simeprevir, sofosbuvir, acunaprevir) and Nucleoside type(mericitabine)The antiviral activity of tegobuvir has been tested in combination with ribavirin and pegylated interferon 2α. Results were positive and there was a significant increase in antiviral activity in the treated patients. Filibuvir underwent clinical trials, however recently was announced the termination of its development by the pharmaceutical company. Similarly, for simeprevir and sofosbuvir. Recent data presented that a triple combination of sofosbuvir, ribavirin and ledipasvir lead to 100% treatment of HCV patients[14]





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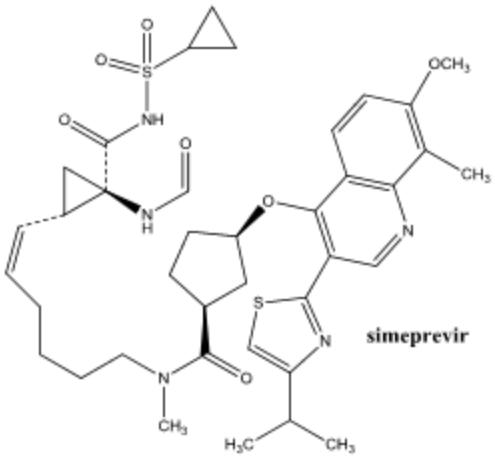

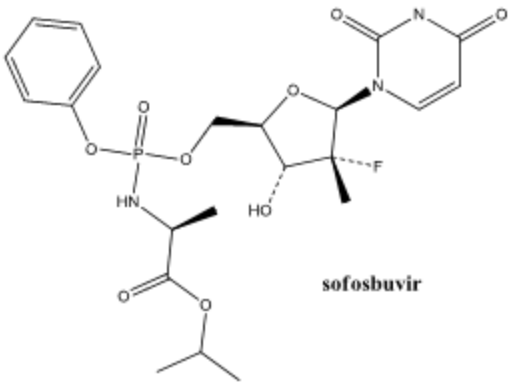

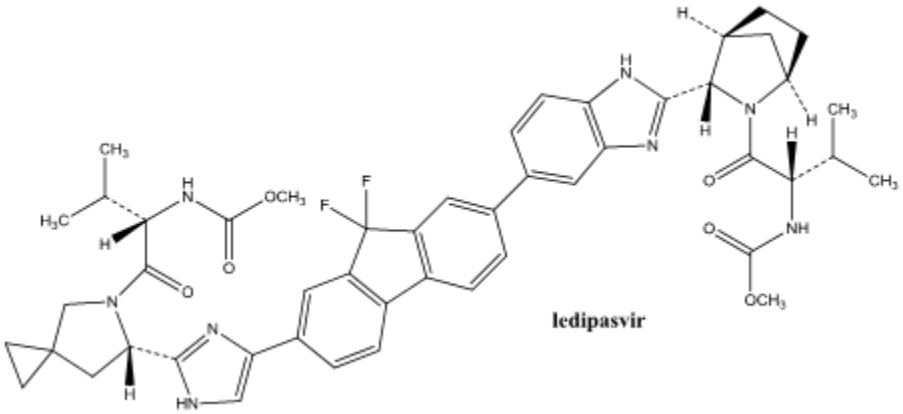

Cyclophilin inhibitors

Cyclophilin has a supporting role in the function of proteins and promotes the replication of HCV virus. In order to treat the disease, we need to inhibit the action ofcyclophilin. Alisporivir is a cyclophilin inhibitor, which can be administered orally and has been tested in HIV/HCV co-infected patients. Nowadays undergoes clinical trials and it is administered in a combination with ribavirin and pegylated interferon 2α with positive results against HCV virus.

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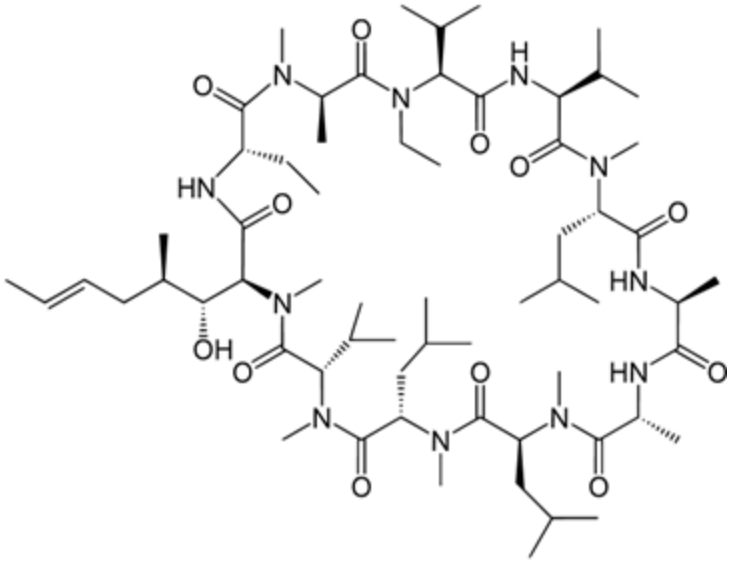

alisporivir

New combination therapies

To increase the therapeutic effect of the used treatment, sometimes a combination of three or more drugs is used. More frequent is the use of two DAA agents together with ribavirin and pegylated interferon 2α. It is found to be very effective in both genotypes (1 and 2) of the patients, which after an interval of 12 weeks they became HCV-RNA negative. Additionally, HCV protease inhibitors, such as boceprevir and telaprevir are combined with ribavirin and PEG interferon 2α, called"triple therapy". However, this type of treatment is difficult to manage group of patients with serious liver fibrosis or liver transplant failure. In clinical trials, is studied the possibility of the treatment of HCV without ribavirin. Data available from the trial, shown that combination of daclastavir with an under development NS3-4A inhibitor BMS-60032, has positive results in the patients infected with genotype 1 of HCV. As far as it concerns new developed interferons, there is one attempt to enter the market pegylated interferon lambda 1. Unlike pegylated interferon 2α, the receptor of this new interferon is expressed in the hepatic cells and as a result, fewer side effects and flu symptoms are present during the treatment.

DISCUSSION

Since 1960's, where the first antiviral drug was developed, a great progress has been made and many useful drugs against many serious viral diseases have been developed. Although antiviral drugs do not kill or remove the virus from the body, they have significantly increased the life expectancy in many lethal diseases, such as hepatitis C and AIDS. Old drugs have, sometimes, presented low efficacy and undesirable side effects and that is the reason why newer and safer antivirals were developed, which also possess broader spectrum of activity. Many substances undergo nowadays clinical trials to be determined whether they could be used as antiviral drugs. Many of them, such as favipiravir, dolutegravir, peramivir have shown great results both in animal testing and in patients. On the other hand, some others need further studies and experiments before authorization and marketing. There are many viral diseases, which could be only prevented by vaccines and not treated with certain drugs. The case of HPV (Human Pappilomavirus) is the most significant. The virus infects the body and stays there during the lifetime and the person presents warts in different parts of its body, *e.g.* genital and common warts. This type of infection is the number one cause for cervical cancer, but could be prevented by vaccines Gardasil and Cervarix. Generally, many vaccines have been developed for many viral diseases, like influenza, yellow fever, hepatitis B and C, which gave the opportunity to protect vulnerable groups of people from been infected by several viruses. Unfortunately, for diseases such as AIDS, there are not any vaccines registered and protection could be achieved by the usage of condoms.

CONCLUSION:

The aim of our work was to present new antiviral drugs that have been developed since 2014 till 2017 or are under clinical trials and to mention older antivirals. New developed drugs have greater efficacy and less side effects that older ones. Thanks to them, the life expectancy has been significantly increased and the quality of life has been improved.

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REFERENCES:

1. MYCEK MJ, HARVEY RA, CHAMPE PC. Pharmacology [online]. 2nd edition. Philadelphia: Lippincot Williams & Wilkins; 1999 [cited 2018 Jan 5]. Avilable from: http://www.pdfdownload4free.com/pharmacology-2nd-edition-by-mary-j-mycek-richard-a-harvey-pamela-c-champe**.**
2. KOONIN EV, SENKEVICH TG, DOLJA VV. The ancient virus world and evolution of cells. Biol Direct [online]. 2006, Sep 19 [cited 2018 Jan 5]; 1:29. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1594570/pdf/1745-6150-1-29.pdf
3. MAGDEN J, KÄÄRIÄINEN L, AHOLA T. Inhibitors of virus replication: recent developments and prospects. Appl Microbiol Biotechnol [online]. 2005 Mar [cited 2018 Jan 5]; 66(6):612–21. Available from: http://link.springer.com/content/pdf/10.1007%2Fs00253-004-1783-3.pdf**.**
4. LWOFF A, HORNE RW, TOURNIER P. A virus system. C R Hebd Seances Acad Sci 1962 Jun 13; 254:4225–7. French.
5. EDWARDS RA, ROHWER F. Viral metagenomics. Nat. Rev. Microbiol [online]. 2005 Jun [cited 2018 Jan 5]; 3(6):504–10. Available from: http://www.nature.com/nrmicro/journal/v3/n6/full/nrmicro1163.html
6. CHAYAVICHITSILP P, BUCKWALTER JV, KRAKOWSKI AC, FRIEDLANDER SF. Herpes simplex. Pediatr Rev. 2009 Apr; 30(4):119–29.
7. ELAD S, ZADIK Y, HEWSON I, HOVAN A, CORREA ME, LOGAN R, ELTING LS, SPIJKERVET FK, BRENNAN MT. A systematic review of viral infections associated with oral involvement in cancer patients: a spotlight on Herpesviridea. Support Care Cancer [online]. 2010 Aug [cited 2018 Jan 5]; 18(8):993–1006. Available from: http://link.springer.com/content/pdf/10.1007%2Fs00520-010-0900-3.pdf**.**
8. DE CLERCQ E. The discovery of antiviral agents: ten different compounds, ten different stories. Med Res Rev [online]. 2008 Nov [cited 2018 Jan 5]; 28(6):929-53. Available from: http://onlinelibrary.wiley.com/doi/10.1002/med.20128/pdf.

9. DE CLERCQ E. Antiviral drugs in current clinical use. J Clin Virol [online]. 2004 Jun [cited 2018 Jan 5]; 30(20):115-33. Available from: http://www.sciencedirect.com/science/article/pii/S1386653204000459**.**

10. DRUG BANK: Open Data Drug & Drug Targets Database. Version 3. [online]. Available from: http://www.drugbank.ca/

11. EIZURU Y. Development of new antivirals for herpes viruses. Antiviral Chem Chemother. 2003 Nov; 14:299-308.

12. DE CLERCQ E. Antiviral drugs: current state of the art. J Clin Virol [online]. 2001 Aug [cited 2018 Jan 5]; 22(1):73-89. Available from: http://www.sciencedirect.com/science/article/pii/S1386653201001676**.**

13. GERSHBURG E, PAGANO JS. Epstein-Barr virus infections: prospects for treatment. J Antimicrob Chemother [online]. 2005 Aug [cited 2018 Jan 5]; 56(2):277-81. Available from: http://jac.oxfordjournals.org/content/56/2/277.full.pdf+html