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CURRENT STATUS OF HIV-1 INTEGRASE INHIBITORS

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ABSTRACT

The treatment of HIV is of prime importance in the developing countries as the threaten of death due to AIDS has been increasing tremendously but with the recent innovations in the field and development of certain chemotherapeutic agents it can be treated and one can increase the life of patient with the help of retroviral therapy. The present review is an attempt made to reveal the importance of integrase inhibitors in the treatment of HIV and recent advances along current status of HIV 1 integrase inhibitors. Highly active antiretroviral therapy (HAART) significantly decreases plasma viral load, increases CD4+ T-cell counts in HIV-1-infected patients and has reduced progression to AIDS in developed countries. However, adverse side effects, and emergence of drug resistance, mean there is still a demand for new anti-HIV agents. The HIV integrase (IN) is a target that has been the focus of rational drug design over the past decade. In 2007, Raltegravir was the first IN inhibitor approved by the US Food and Drug Administration for antiretroviral combination therapy, while another IN inhibitor, Elvitegravir, is currently in Phase III clinical trials. This article reviews the development and resistance profiling of small molecule HIV-1 IN inhibitors.

Key-words: Antiretroviral, HIV, integrase, inhibitors.

INTRODUCTION:

Integrase inhibitor:

Integrase inhibitors are a class of antiretroviral drug designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell. Since integration is a vital step in retroviral replication, blocking it can halt further spread of the virus. Integrase inhibitors were initially developed for the treatment of HIV infection, but they could be applied to other retroviruses. The first integrase inhibitor approved by the U.S.

Food and Drug Administration (FDA) was raltegravir (brand name Isentress), approved on October 12, 2007. Research results published in the New England Journal of Medicine on July 24, 2008, concluded that "raltegravir plus optimized background therapy provided better viral suppression than optimized background therapy alone for at least 48 weeks." Since integrase inhibitors target a distinct step in the retroviral life cycle, they may be taken in combination with other types of HIV drugs to minimize adaptation by the virus. They are also useful in salvage therapy for patients whose virus has mutated and acquired resistance to other drugs. [1]

Acquired immunodeficiency syndrome (AIDS), caused by infection from the human immunodeficiency virus type 1 (HIV-1), remains a serious global health problem. After years of hard work, a number of inhibitors of reverse transcriptase (RT) and protease (PR) were discovered and introduced in clinical practice. Unfortunately, all the mono therapies using either RT or PR inhibitors have failed owing to the rapid emergence of HIV-resistant strains, and the long-term goal of eradicating the virus from infected cells is still unattained. However, the use of combinations of both RT and PR inhibitors has resulted in significant increases in disease-free survival. This multiple attack is more effective, blocking two different steps of the virus replication cycle and causing a delay in the emergence of resistant strains. Therefore, it is evident that the development of new inhibitors targeted toward other viral proteins is of paramount importance. A further viral protein as potential target for antiretroviral therapy is HIV-1 integrase (IN). Recently, anti-IN agents in combination with RT and PR inhibitors have been found to be synergistic in vitro assays and a combination therapy that uses inhibitors of all three enzymes at the same time could result in a real breakthrough in the HIV-1 therapy. Unfortunately, no inhibitor of HIV-1 IN is currently used in clinical practice, and this fact led us to make greater efforts in research in this field. The full-length HIV-1 IN (288 amino acids) has three domains: the catalytic core, the C-terminal and the N-terminal domains. It is thought that the catalytic core contains the active site responsible for catalysis of all the reactions of integration. Three amino acids (Asp64, Asp116, and Glu152) in the catalytic core domain are highly conserved among retrotransposon and retroviral INs. Mutation of these residues generally leads to a loss of all the catalytic activities of these proteins, and they are therefore thought to be essential components of the IN active site. The catalytic core domain socked with 5-chloroindolyltetrazolylpropenone (5CITEP) (a potent inhibitor of IN reported by Shionogi Company) was resolved by D. Davies. The crystal structure shows a dimeric model in which two monomers interact with each other, but actually it is not clear whether IN works in vivo as a monomer, a dimer, or a tetramer. Multiple steps in the integration process are catalyzed by HIV-1 IN, as shown schematically in Fig. 1. The integration of HIV-1 DNA into the host chromosome is achieved by the IN performing a series of DNA cutting and joining reactions (A–C). The first step in the integration process is 3′ processing, in which the enzyme removes two nucleotides from each 3′ end of the proviral DNA, leaving recessed CA OHs at the 3′ ends. Moreover, IN cuts the human DNA at the site of integration 5 bases apart (Fig. 1A).

In a second step, termed “strand transfer”, the IN protein joins the previously processed 3′ ends to the 5′ ends of strands of target DNA at the site of integration (Fig. 1B). Finally, in the 5′ end, the joining IN fills in the gaps and ligates the unjoined strands (Fig. 1C). (1)

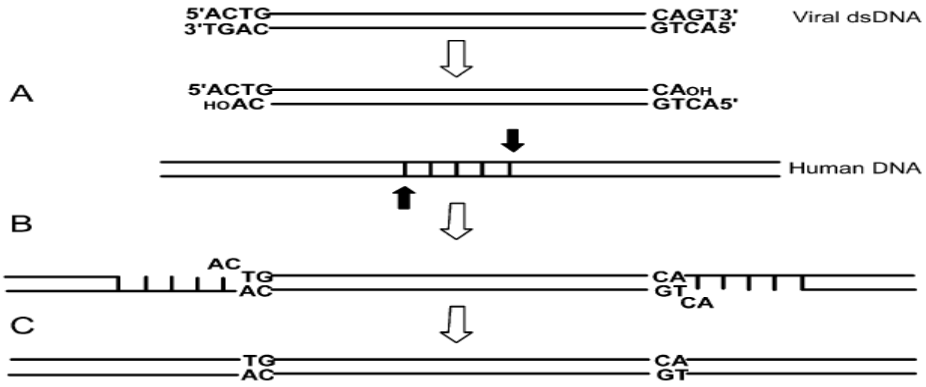

Fig. no. 1 Schematic steps for HIV-1 integration

HISTORY:

In the 1980s an infectious disease started to plague human civilization. The coexistence of viruses and humans is a fight for survival for both because the invaders can kill the human but in doing so eliminate their own host. The body uses its immune system to protect it from bacteria, viruses and other disease-causing beings, and when it fails to do so immunodeficiency diseases occur. One such disease is acquired immunodeficiency syndrome (AIDS) which is most commonly a result of an infection by the human immunodeficiency virus (HIV). [2] Two closely related types of HIV have been identified, HIV-1 and HIV-2. While HIV-2 is spreading in India and West Africa, HIV-1 is more virulent and the number one cause of AIDS worldwide. Though some of the patients have different results in most cases people infected with HIV go on to develop AIDS and ultimately die of opportunistic infections or cancer. Integration to the retroviral genome is critical for gene expression and viral replication. The viral genome is reversely transcribed into the DNA of the infected cell by viral reverse transcriptase; the DNA is then integrated into the host-cell chromosomes with the aid of the viral integrase. RNA transcripts are produced from integrated viral DNA and serve both as mRNAs to direct the synthesis of viral proteins and later as RNA genomes of the new viral particles. Viral particles escape from the cell by budding from the plasma membrane, each enclosed in a membrane envelope. In this process HIV-1 integrase is essential and therefore a very promising target for anti-AIDS drug design. [3] Selective drug design is a possibility as HIV-1 integrase has no known cellular equivalent. Many integrase inhibitors have been discovered and designed but only a few of the molecules were developed further and got as far as phase II or phase III of clinical trials. Raltegravir (brand name Isentress®) was granted accelerated approval from FDA in October 2007 and from EMEA (now EMA) in December 2007.[4, 5] It was marketed as an antiretroviral drug (ARV) for

HIV-1 infected adults who had already been exposed to a minimum of three ARV classes and showed multi-drug resistance. In general there are two main groups of integrase inhibitors; Integrase Strand Transfer inhibitors (INSTI) and Integrase Binding Inhibitors (INBI). INSTIs restrain the binding of pre-integration complex (PIC) and host DNA and INBIs restrain integrase and viral DNA binding. Raltegravir is an INSTI integrase inhibitor which inhibits both HIV-1 and HIV-2 replication. It is more potent than other previously known integrase inhibitors as well as causing fewer side effects. Raltegravir is currently the only HIV-1 integrase inhibitor being used to treat HIV infections but other drugs are in clinical trials, e.g. Elvitegravir and S/GSK1349572.

The HIV-1 integrase enzyme

The HIV-1 integrase (IN) is a key enzyme in the replication mechanism of retroviruses. It is responsible the for transfer of virally encoded DNA into the host chromosome which is a necessary event in retroviral replication. Since IN has no equivalent in the host cell, integrase inhibitors have a high therapeutic index as they do not interfere with normal cellular processes

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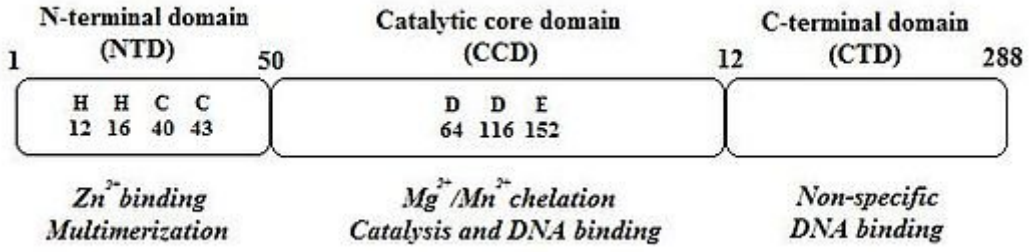

Fig. no. 2: Structural domains of the HIV-1 integrase

IN belongs, both mechanistically and structurally, to the super family of polynucleotidyl transferases 10 and is composed of 288 amino acids that form the 32 kDa protein. Retroviruses encode their enzymes (protease, reverse transcriptase and integrase) with the POL gene with the 3´end encoding for IN. [6]

IN is composed of 3 structurally independent, functional domains

1. The N-terminal domain (NTD) encompasses amino acids 1-50 and contains two histidine residues (His12 and His16) and two cysteine residues (Cys40 and Cys43), all of which are absolutely conserved and form a HHCC zinc-finger motif. Single mutations of any of these four residues reduce IN enzymatic activity. The HHCC zinc-finger motif chelates one zinc atom per IN monomer. The NTD is required for higher order multimer formation which appears to be its primary role. The multimerization requires zinc atom that stabilizes the fold.

2. The catalytic core domain (CCD), which encompasses amino acids 51- 212, contains the active site of IN but it can´t catalyze integration in the absence of NTD and CTD (the C-terminal domain). CCD contains three absolutely conserved negatively charged amino acids; D64, D116 and E152. These amino acids form the DDE motif that coordinates divalent metal ions (Mg2+ or Mn2+).

These metal ions are essential for the catalysis of integration. CCD has a mixed β and α structure with five β-sheets and six α helices that are linked by flexible loops.

The flexible loops allow conformational changes that are required for 3´processing of the viral DNA and strand transfer (STF) reactions which are two key steps of the integration reaction. CCD is essential for these steps and substitution of any of the residues in the DDE motif dramatically inhibits the activity of IN.

3. The C-terminal domain (CTD), which encompasses amino acids 213-288, binds DNA nonspecifically and its interaction with NTD and CCD is required for IN 3´-processing and strand-transfer activities. CTD is the least conserved of the three domains. IN acts as a multimer and dimerization is required for the 3´-processing step, with tetrameric IN catalyzing the strand-transfer reaction. [6]

Function of HIV-1 integrase:

HIV-1 integration occurs through a multistep process that includes two catalytic reactions:

3´endonucleolytic processing of proviral DNA ends (termed 3´processing) and integration of 3´-processed viral DNA into cellular DNA (referred to as strand transfer).[7] In 3´processing IN binds to a short sequence located at either end of the long terminal repeat (LTR) of the viral DNA and catalyzes endonucleotide cleavage. This results in elimination of a dinucleotide from each of the 3´ends of the LTR. Cleaved DNA is then used as a substrate for integration or strand transfer.

Strand transfer is a trans-esterification reaction involving a direct nuleophilic attack of the 3´hydroxy group of the two newly processed viral 3´-DNA ends on the phosphodiester backbone of the host target DNA. This leads to covalent insertion of viral DNA into the genome of the infected cell. Strand transfer occurs simultaneously at both ends of the viral DNA molecule, with an offset of precisely five base pairs between the two opposite points of insertion.

The integration reaction is completed by removal of unpaired dinucleotides from the 5'- ends of the viral DNA, repair of the single-stranded gaps created between the viral and target DNA molecules and ligation of 3'-ends to 5'-ends of the host DNA. Divalent metals, Mg2+ or Mn2+, are required for 3'-processing and strand transfer steps as well as for assembly of IN onto specific viral donor DNA to form a complex that is competent to carry out either function. Because Mg2+ abundance over Mn 2+ is 1,000,000-fold in cells it's a more reasonable cofactor for integration.

Mechanism of action:

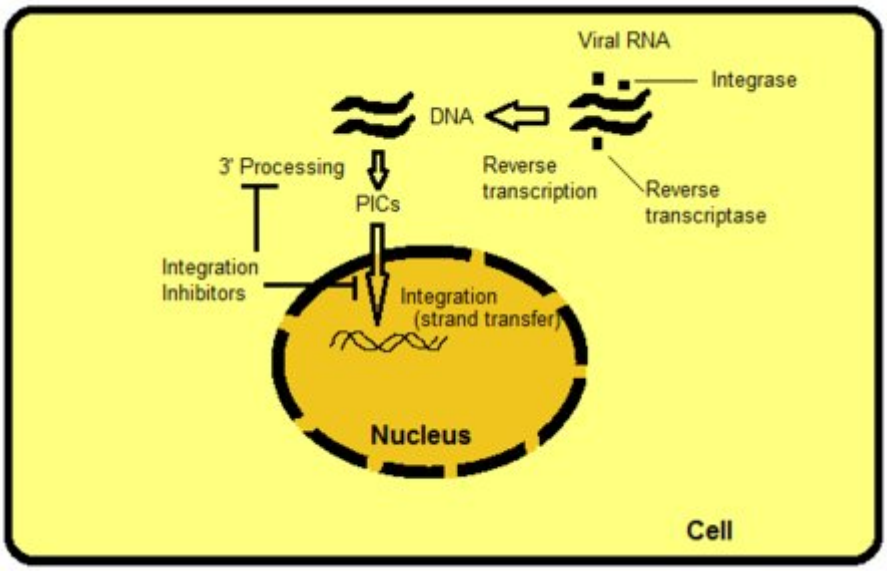

Fig. no. 03: Integration of viral RNA into host cell DNA

There are several ways to target integrase but strand transfer inhibition is the most common one. Other targets include, for example, the protein domains beyond the active site of IN. The domains interact with viral or host DNA and are important for binding to the enzyme. It is possible to hamper functions of the enzyme by disrupting or removing these bindings. PIC is a multimeric protein structure inside the host cell, composed of both viral and host proteins. Integrase is a part of PIC‘s viral component. PIC‘s viral and host proteins are believed to modulate intrinsic activity of the enzyme, shuttle PIC to the nucleus and direct integration of viral DNA into a transcriptionally active region of the host genome. If it were possible to exclude certain proteins from the PIC it would block the ability of the virus to integrate into the host genome. The process where the retroviral RNA is transcribed to DNA and then integrated into the host cell's genome is shown in figure 3.

IN strand transfer inhibitors (INSTIs)

Mg2+ and Mn2+ are critical cofactors in the integrase phase and if they are chelated it can cause functional impairment of IN. This gives the opportunity to design and develop highly efficient IN inhibitors (INIs). In fact, all small molecule HIV-1 INIs that are now being researched contain a structural motif that coordinates the two divalent magnesium ions in the enzyme’s active site. Raltegravir and elvitegravir share the same mechanism of action against integrase which is to bind to the active site of Mg2+ ions. Inhibitors compete directly with viral DNA for binding to integrase in order to inhibit 3‘-end processing.In doing this the inhibitors completely block the active site from binding to target DNA.

This way of inhibitions is called strand transfer inhibition.

Inhibition of the LEDGF/p75- integrase interaction

Lens epithelial derived growth factor is a host protein that binds to integrase and is crucial for viral replication. The mechanism of action is not precisely known but evidence suggest that LEDGF/p75 guides integrase to insert viral DNA into transcriptionally active sites of the host genome. Inhibitors of this protein are already being developed and patented. They are likely to be highly target specific and less prone to the development of resistance.

IN binding inhibitors

Another class of INIs could be IN binding inhibitors (INBIs) such as V-165. V-165 is a compound shown to inhibit integration but without obvious effect on viral DNA synthesis. When the mechanism of action was studied it showed that V-165 interferes with viral DNA-IN complex formation. Due to its interfering action it is classified as an IN binding inhibitor. Other compounds, such as styrylquinolines share similar mechanism by competing with the LTR substrate for IN binding (3)

Drug design

Binding

INSTIs bind tightly and specifically to the IN that is associated with the ends of the DNA by chelating the divalent metal ions (Mg2+) which is coordinated by the catalytic triad i.e. the DDE motif. The DDE motif is located in the CCD of IN and is the active site of the enzyme and hence INSTIs are so called active site inhibitors. INSTIs bind to a specific site close to the DDE motif of IN, a site that is present only in the conformation that occurs after processing of the 3´ viral DNA ends. Viral DNA may well form a part of the inhibitor binding site. The binding is a form of allosteric inhibition as it implies blockage of a specific integrase-viral DNA complex. This results in selective inhibition of the strand-transfer reaction, with no significant effect on the 3´-processing reaction. INSTIs may therefore be more specific and bind selectively to the target DNA binding site and hence be less toxic than bi functional inhibitors that are able to bind to both the donor and target binding sites. [8]

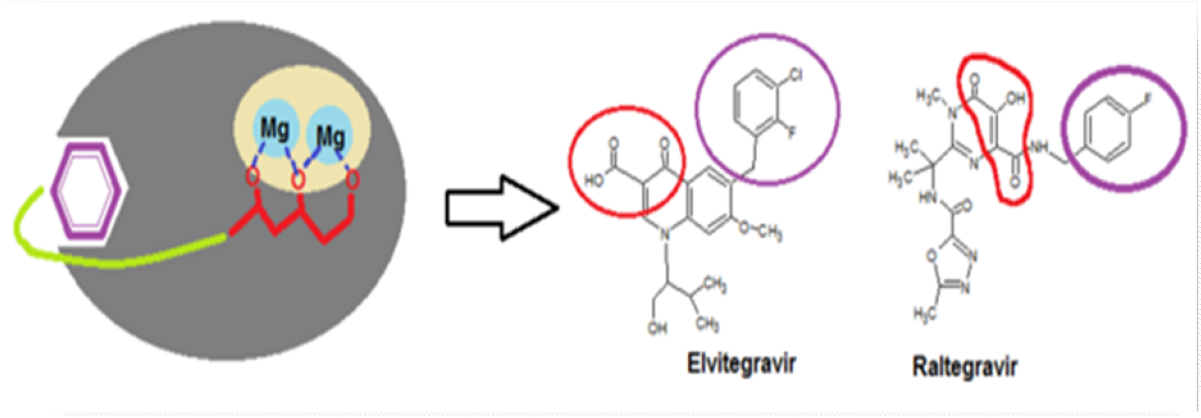

Fig. no.4: Structure activity relationship of elvitegravir and raltegravir. A benzyl group in a hydrophobic pocket and a triad to chelate the two Mg2+ ions.

Two structural components are necessary for integrase binding:

A hydrophobic benzyl moiety that buries into a highly hydrophobic pocket near the active site; and chelating triad that binds with two Mg2+ ions in a rather hydrophilic region, anchoring the inhibitor onto the protein surface. In fact, all potent integrase inhibitors possess a substituted benzyl component that is critical for maintaining 3'end joining potency. Removal of the benzyl group prevents inhibitory function. Lipophylic substituents are therefore beneficial for the strand transfer inhibition, in particular the thiophenyl, furanyl and (thiophen-2-yl)phenyl substitutions. Heteroaromatic amine and amide also cause increase in 3' processing inhibitory action

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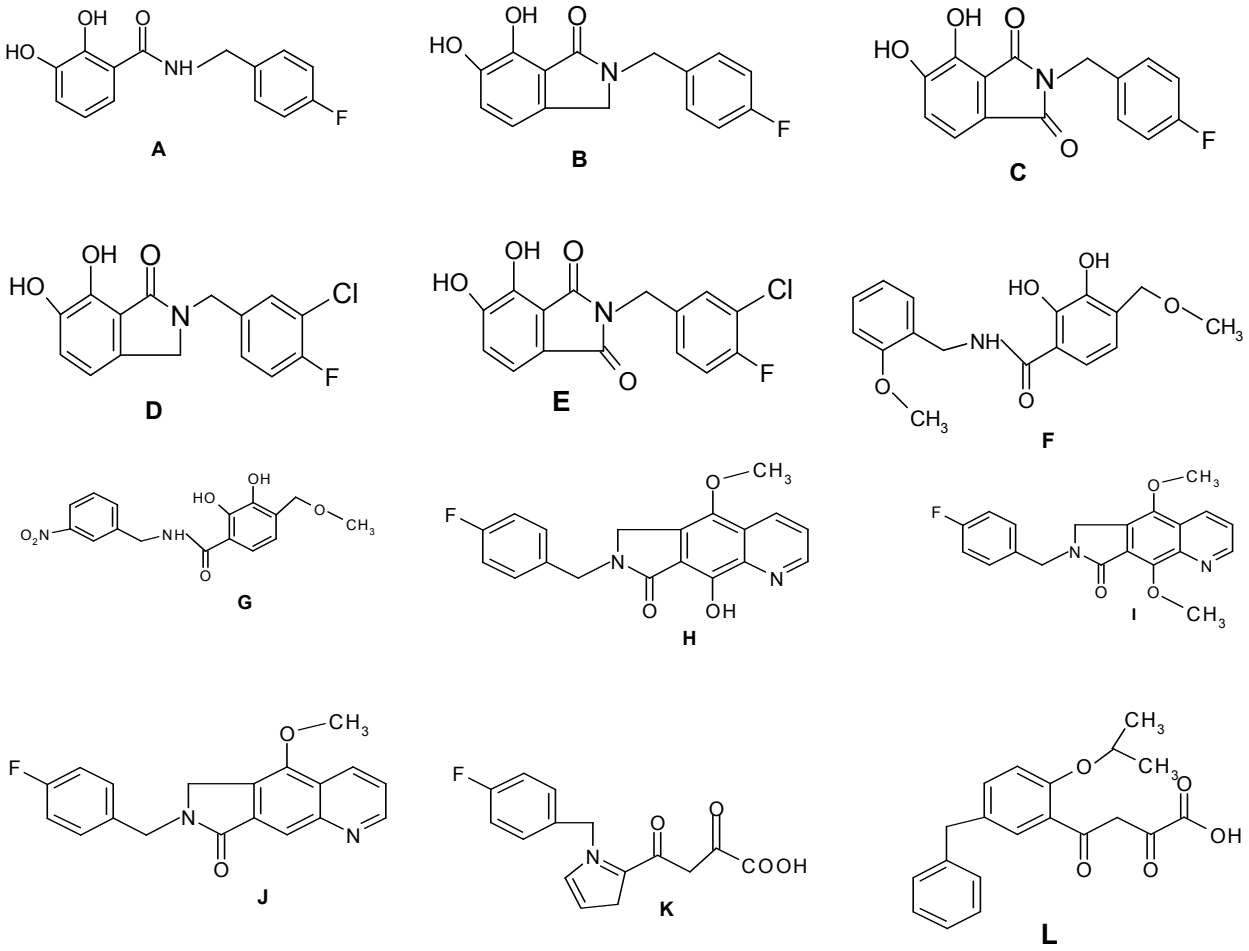

Fig. no. 5: Examples of integrase inhibitors.

When catechol-based inhibitors of IN were researched it was observed that maintaining a planar relationship with the bis-hydroxylated aryl ring increases potency. The inhibitory activity could be further optimized by including a meta-chloro substituent, enhancing the interaction of the benzyl group with the adjacent hydrophobic pocket. A benzyl substituted hydroxyl group improves metal-chelating capability while a methoxy group (I) is much less potent due to steric clash by the additional methyl group with the catalytic metals. When researching diketo derivates,

the central pyrrole ring of structure K in fig. 5 was replaced by a series of aromatic systems having various substitution patterns. That provided optimum relative orientation of the benzyl and diketoacid (DKA) site chain. Structure L in fig. 5 resulted in 100 fold increase in potency. Synthesized INIs with a quinoline subunit and an ancillary aromatic ring linked by functionalized spacers such as amide, hydrazide, urea and hydroxyprop-1-en-3-one moiety. They found that the amide group containing dervates were the most promising ones.By synthesizing series of styrylquinones researchers found out that a carboxyl group at C-7, a hydroxylgroup at C-8 in the quinoline subunit and an ancillary phenyl ring (Figure 5: Structure M) are required for inhibition, although alterations of the ring are tolerated. Two hydroxyl groups on the ancillary phenyl ring are also required for inhibitory potency.

Pharmacophore:

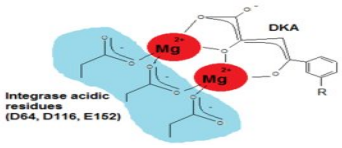

Fig. No. 6: Binding of DKAs to DDE amino acids residues of integrase

Since critical structure information is scarce on HIV integrase catalysis it is difficult to find the exact pharmacophore for its inhibition. By studying the SAR and pharmacophore of a dual inhibitor scaffold, focusing both on integrase and reverse transcriptase (RT) it would be possible to observe anti-integrase activity. [8] By studying the SAR of HIV integrase inhibitors it was possible to find that for optimal integrase inhibition the pharmacophore requires a regiospecific (N-1) DKA of a specific length. DKA functionality or its heterocyclicbioisostere that selectively inhibit strand transfer seem to be present in all major chemotypes of integrase inhibitors. As detailed in the SAR discussion above the two necessary structural components of INI are a benzyl hydrophobic moiety and a chelating triad to bind the Mg2+ ions. For the triad to bind the Mg2+ ions has to be ionized and thus a Pharmacophore bioisostere has to be ionized too and the benzyl Pharmacophore bioisostere must to be very hydrophobic. However, despite previous success in clinical development (raltegravir), a detailed binding model is lacking so it has proven difficult to structure base the design of integrase inhibitors. When the Pharmacophore of salicylic acid and catechol were merged, new chemical scaffolds were created. The adjacent hydroxyl and carboxylic groups on salicylic acid could bind with the metal ions and serve as their pharmacophore. Polyhydroxylated aromatic inhibitors are mostly active against strand transfer reactions and 3‘-processing which suggests a mechanism that targets both steps. This is a very important part of the compound as it can be used to bind to the divalent metal on the active site of IN and as such be effective against viral strains that are resistant to strand transfer specific inhibitors.

Resistance

It has been discovered that over 60 variations of INSTI mutations cause in vivo and in vitro resistance. Due to these mutations and development of resistance the inhibitors are less effective against the virus. Resistance of INI corresponds to those of

other ARV drugs. First IN resistance is caused by primary mutations that decrease INI sensitivity in combination with secondary mutations that further reduce virus sensitivity and/or repair decreased fitness of the virus. Secondly there is a genetic barrier to INI resistance, defined by the number of mutations required for the loss of clinical INI activity. Thirdly there is extensive but incomplete cross-resistance among the INIs. A loop containing amino acid residues 140-149 is located in the catalytic-core domain and is important for IN function as mentioned before. This loop is flexible and even though its role is not quite known it is thought to be important and its functions critical for DNA binding. This resistance appears within mutations in this IN-coding region. The resistance to raltegravir and elvitegravir is primarily due to the same two mutation pathways but other primary mutations are also involved for each of the drugs. Some mutations increase resistance to the drugs to a large extent than others. For example one of the most common mutation pathway increases the resistance to raltegravir up to 100 times more than the second most common one. Resistance to Integrase Inhibitor S/GSK1349572 is still being developed and the resistance has not been fully characterized. When it was assessed alongside the primary mutations of raltegravir and elvitegravir it did not show cross-resistance which means that it could be useful against drug resistant viruses. Raltegravir has limited intestinal absorption and thus resistance cannot be overcome by prescribing higher doses. Newer drugs are warranted to overcome this pharmacological disadvantage and gain plasma concentrations high enough to target raltegravir-resistant viruses. [9]

Current status

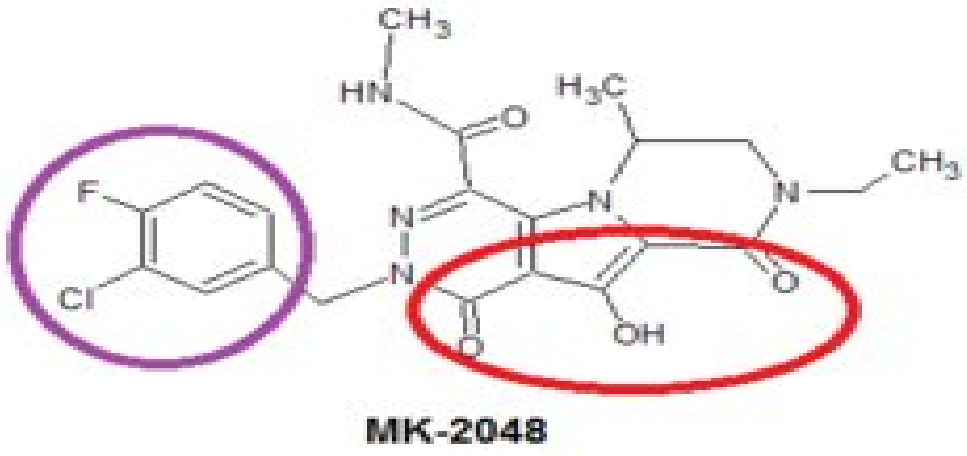

Fig. no.7: Structure of MK-2048 with important Pharmacophore highlighted

The search for new ways to improve treatment of patients infected with HIV is constant. Considering the experience that has been gathered since the 1980s of ARV drug development arrival of INSTIs as a new potent class of ARV signals a new era in the treatment of HIV. Development of a successful INSTI treatment was accomplished when raltegravir was discovered by Merck Sharp & Dohme Limited.

A conditional marketing authorization was licensed in December 2007 by the European Commission which was valid throughout the European Union. In 2009 this authorization was converted to a full marketing authorization and in the same year the FDA changed the approval from accelerated to traditional approval and listed the drug as a first line ARV treatment agent. The second INSTI drug, elvitegravir, was identified by Japan Tobacco and clinical trials began in 2005. In 2011 the drug was still in phase three clinical trials, where it is being compared to raltegravir, in treatment experienced subjects and is also in phase two development in naïve subjects as a part of a multidrug treatment. S/GSK1349572 is a integrase inhibitor discovered by ViiV /Shinongi which was entering phase three in clinical trials in 2011. This new drug is promising and seems to be well tolerated and so far shows better results than both Raltegravir and Elvitegravir. Since there have been problems with resistance to Raltegravir and Elvitegravir, scientists have started to work on new second generation integrase inhibitors, such as MK-2048 which in 2009 was developed by Merck. It's a prototype second generation INSTI that remains potent against viruses containing mutations against Raltegravir and Elvitegravir. The mechanism of action and SAR of MK-2048 is the same as of the other INSTIs, the structure of MK-2048 shown in figure 6 with essential Pharmacophore highlighted. Even though drugs discussed above are promising the development has a long way to go and many things are still unknown about the efficacy, safety and mechanism of action of these drugs.

1. Raltegravir

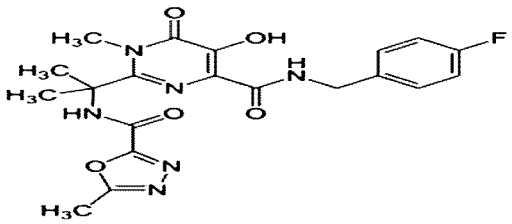

Fig. no. 8: Structure of Raltegravir

Raltegravir is N-(2-(4-(4-fluorobenzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan-2-yl) Raltegravir (MK-0518, brand name Isentress) is an antiretroviral drug produced by Merck & Co., used to treat HIV infection. It received approval by the U.S. Food and Drug Administration (FDA) in October 2007, the first of a new class of HIV drugs, the integrase inhibitors, to receive such approval. In December 2011, it received FDA approval for pediatric use in patients ages 2-18, taken in pill form orally twice a day by prescription with two other antiretroviral medications to form the cocktail (most anti-HIV drugs regimens for

adults and children use these cocktails). Raltegravir is available in chewable form but- because the two tablet formulations are not interchangeable- the chewable pills are only approved for use in children two to 11. Older adolescents will use the adult formulation. [10]

Research

Raltegravir significantly alters HIV viral dynamics and decay and further research in this area is ongoing. In clinical trials patients taking Raltegravir achieved viral loads less than 50 copies per millitre sooner than those taking similarly potent Non-nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors. This statistically significant difference in viral load reduction has caused some HIV researchers to begin questioning long held paradigms about HIV viral dynamics and decay. Research into Raltegravir's ability to affect latent viral reservoirs and possibly aid in the eradication of HIV is currently ongoing.[11]

Research results were published in the New England Journal of Medicine on July 24, 2008. The authors concluded that "raltegravir plus optimized background therapy provided better viral suppression than optimized background therapy alone for at least 48 weeks."

Research on human cytomegalovirus (HCMV) terminase proteins demonstrated that Raltegravir may block viral replication of the herpesviruses.

Tolerability

Raltegravir was generally well tolerated when used in combination with optimized background therapy regimens in treatment-experienced patients with HIV-1 infection in trials of up to 48 weeks' duration.

2. Elvitegravir

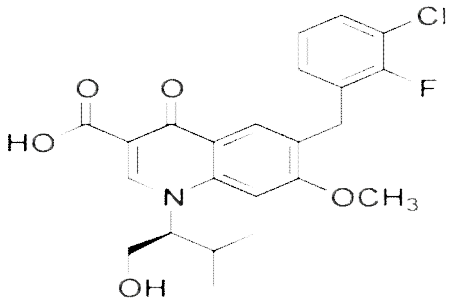

Fig. no. 9: Structure of Elvitegravir

Elvitegravir is 6-[(3-Chloro-2-fluorophenyl) methyl]-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxoquinoline-3-carboxylic acid

Elvitegravir (EVG) is an investigational new drug for the treatment of HIV infection. It acts as an integrase inhibitor. It is undergoing Phase III clinical trial conducted by the pharmaceutical company Gilead Sciences, which licensed EVG from Japan Tobacco in March 2008. According to the results of the phase II clinical trial, patients taking once-daily elvitegravir boosted by Ritonavir had greater reductions in viral load after 24 weeks compared to individuals randomized to receive a Ritonavir-boosted protease inhibitor. [12]

CONCLUSION

As the importance of HIV1 integrase inhibitors remains unresolved in the treatment of HIV and AIDS most of the times retroviral therapy finds certain limitations in the treatment of HIV resistant strains. The newer class of HIV 1 integrase inhibitors may prove as an effective tool in the treatment of HIV and AIDS. In recent days the HIV 1 integrase inhibitors getting more importance in the treatment of HIV and AIDS.

Most of the research work in the field of drug design has been directed towards the development of newer derivatives of Raltegravir and Elvitegravir in recent advances some members of this class are currently in clinical trials which may come in market in future. As a new class of drug targeting the third essential enzyme for HIV replication (along with reverse transcriptase and protease), the integrase inhibitors are a welcome addition to the treatment armamentarium for HIV/AIDS in treatment-experienced patients failing available antiretroviral regimens. Clinically relevant interactions with other available antiretroviral agents and long-term adverse effects and tolerability will have an impact on the future clinical value of the integrase inhibitors.

Definition of the genetic barriers to integrase-inhibitor resistance, determinants of choice in the divergent pathways to resistance, and questions regarding cross resistance across the class will need to be addressed. The integrase inhibitors should also be studied further as potential components in first-line HAART regimens based on available experimental data with raltegravir in combination with NRTIs. This would be particularly true for those in whom PI- or NNRTI-based therapy may be less than optimal. Finally, further safety, pharmacokinetic, and tolerability studies of raltegravir in special populations are warranted.

When considered as a whole, the promising efficacy and tolerability profile of the integrase inhibitors, absence of cross-resistance with other antiretroviral classes, and demonstrated synergism of the integrase inhibitors in combination with approved antiretroviral agents place the minimum a position to become important components of effective combination antiretroviral regimens in individuals living with HIV/AIDS

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