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Anti-HIV Drug Discovery, Development and Synthesis of Delavirdine: Review Article

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Authors' contributions

This work was carried out in collaboration between both authors. Author WB wrote the protocol and wrote the first draft of the manuscript. Author MJ managed the literature searches and writing drafts of manuscript. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Viruses are the smallest infectious agents of animal and plant tissues. Viruses are totally dependent on living cells to survive as they utilize the host cell's own replication processes, in order to reproduce themselves. HIV is the causative agent of AIDS. HIV is an unusually difficult to treat because it incorporate its own genetic material into the genome of an infected host cell. It infects T cells that carry the CD4 antigen on their surface. Binding and fusion, reverse transcription, integration, transcription, assembly and budding are the major steps of the HIV life cycle. The HIV/AIDS disease is treated by interrupting the HIV life cycle with specially designed drugs. The discovery of effective drugs against HIV has focused on targeting various critical components of the replication cycle of HIV. Depending on the target within the HIV replicative cycle they interact with, anti-HIV compounds are categorized into six groups. These are: nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), cell entry inhibitors or fusion inhibitors (FIs), co-receptor inhibitors (CRIs) and integrase inhibitors (INIs). The development of effective anti-HIV drugs is difficult due to wide

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variations in nucleotide and amino acid sequences. The development of anti-HIV drug passes through several important steps. This includes development from α-APA to ITU, ITU to DATA, DAPY to etravirine. Fosdevirine, lersivirine and rilpivirine are among the drugs that were undergoing clinical development and finally only rilpivirine was approved by FDA. The synthesis of delavirdine employs the use of heterocyclic rings like substituted pyridine and indole.

Keywords: Human immunodeficiency virus; HIV life cycle; anti-HIV drugs and delavirdine.

1. INTRODUCTION

Viruses are the smallest infectious agents of animal and plant tissues. They range in size from 20 to 300 nm. To cause a disease, viruses must enter living cells, unlike bacteria which are able to survive outside cells. Viruses are totally dependent on living cells to survive as they utilize the host cell's own replication processes, in order to reproduce themselves. Human immunodeficiency virus (HIV) and human hepatitis C virus (HCV) infections are chronic and pandemic illnesses that have increased the global burden of health immensely and represent serious public health problems. HIV the causative agent of AIDS, was identified in 1983 following the first reported cases of Acquired Immunodeficiency Syndrome (AIDS) in 1981 and 1982. According to a 2012 UNAIDS report on the global AIDS epidemic, about 34 million people were living with HIV, 2.5 million had acquired new HIV infections and 1.7 million had died of HIV related causes worldwide during 2011[1].

HIV is a member of a class known as retroviruses. These viruses store their genetic information as ribonucleic acid (RNA), unlike most viruses which store their genetic information as deoxyribonucleic acid (DNA). Before viral replication can take place, the RNA must be converted to DNA by reverse transcription, hence the Latin term Retro, meaning 'turning back'[2].

From a medical and pharmaceutical perspective, HIV is an unusually difficult opponent. It belongs to the family of retroviruses, and as such incorporates its own genetic material into the genome of an infected host cell. In this way, the virus can hide from the immune system and engage in a relentless war of attrition with the immune cells. In addition to its capacity to hide, HIV also has a high proliferation rate and an extraordinarily high inherent mutation rate. Thus, the virus is capable of quickly adapting to new conditions, for example by becoming resistant to drugs. Resistant HIV strains against all of the currently available anti-HIV drugs already exist. A new generation of anti-HIV drugs must therefore be effective not only against the wild-type virus, but also against resistant virus strains and preferably have high resilience to new mutations. This adds to the difficulties of drug development against HIV [3].

Today two types of HIV, type 1 (HIV-1) and type 2 (HIV-2) are known. Both originate from non-human primates in Central and West Africa, and were transmitted to humans on several occasions. HIV-1 is responsible for the global epidemic. HIV-2 also causes AIDS, but has a longer latency phase and lower morbidity. Due to its lower infectivity it is not as widely spread [3,4].

The HIV life cycle encompasses several crucial steps, starting from the attachment of the virus to the host cell membrane and finishing with the release of progeny virions from the cell. The HIV life cycle commences by a specific interaction between the virion glycoprotein gp120 on the outer membrane and the CD4 receptor on the host cell surface. This reaction results in a conformational change allowing the interaction of gp120 with the chemokine coreceptor CXCR4 or CCR5. This is then followed by further conformational changes that expose a fusogenic peptide, which anchors into the host cell membrane. Once the viral envelope and cell membrane have fused, the virion is decapsidated releasing the viral RNA into the host cell's cytoplasm. Through the reverse transcription, the viral RNA is transcribed to viral double-stranded DNA. This process is catalyzed by an RNA-dependent DNA polymerase, also known as reverse transcriptase, which is encoded by the viral genome. The viral DNA is then integrated into the host chromosome, and after transcription and translation into viral proteins using the cells' machinery, the assembly of the polyproteins occurs near the cell membrane. During viral assembly, two copies of single-stranded viral RNA are incorporated into the virion, which then buds off from the cell, taking with it part of the host cell membrane. Soon after budding, viral protease cleaves the polyprotein to generate a

mature, functional virion. Generally, antiviral drugs could, in principle, be targeted at either viral proteins or cellular proteins. The first approach is likely to yield more specific, less toxic compounds, with a narrow spectrum of activity and a higher likelihood of virus drug resistance development. The second approach, however, might afford anti-HIV drugs with a broader activity spectrum and less chance of resistance but higher likelihood of toxicity [5,6].

Anti-HIV compounds have been formally approved for clinical use in the treatment of AIDS. These compounds fall into different categories, depending on the target within the HIV replicative cycle they interact with. In all, there are six categories: nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), cell entry inhibitors or fusion inhibitors (FIs), co-receptor inhibitors (CRIs) and integrase inhibitors (INIs) [7].

1.2 Objective of the Review

1.2.1 General objective

The overall objective of the review is to understand the anti-HIV drugs discovery and development.

1.2.2 Specific objectives

- To describe the HIV life cycle stages
- To deal about the anti-HIV drugs discovery
- To describe how anti-HIV drugs are developed through gradual stages
- To describe the synthesis of delavirdine

2. HIV LIFE CYCLE

Human immunodeficiency virus (HIV) and its subtypes are retroviruses and the etiologic agents of AIDS. Human retroviruses were unknown until the 1980's, though animal retroviruses such as feline leukemia virus had been detected previously. HIV belongs to a large family of ribonucleic acid (RNA) lentiviruses. These viruses are characterized by association with diseases of immunosuppression or central nervous system involvement and with long incubation periods following infection before manifestations of illness become apparent [4].

HIV infects T cells that carry the CD4 antigen on their surface. The infection of the virus requires fusion of the viral and cellular membranes, a process that is mediated by the viral envelope glycoprotein (gp120, gp41) and receptors (CD4 and coreceptors, such as CCR5 or CXCR4) on the target cell. As the virus enters a cell, its RNA is reverse-transcribed to DNA by a virally encoded enzyme, the reverse transcriptase (RT). The viral DNA enters the cell nucleus, where it is integrated into the genetic material of the cell by a second virally encoded enzyme, the integrase. Activation of the host cell results in the transcription of the viral DNA into messenger RNA, which is then translated into viral proteins. HIV protease, the third virally encoded enzyme, is required in this step to cleave a viral polyprotein precursor into individual mature proteins. The viral RNA and viral proteins assemble at the cell surface into new virions, which then bud from the cell and are released to infect another cell. The extensive cell damage from the destruction of the host's genetic system to the budding and release of virions leads to the death of the infected cells [8].

The major receptor that facilitates binding of HIV to human Cells is the CD4 differentiation molecule. Following HIV infection there is progressive depletion and/or dysfunction of CD4+ T lymphocytes that results in immunodeficiency. A viral surface glycoprotein known as gp120 binds to the CD4 molecule. On binding, a conformational change occurs in the gp120-CD4complex that allows gp120 to interact with one or more cellular co-receptors. The gp120-co-receptor interaction triggers a further conformational change in gp41, another of the viral surface structures; hydrophobic portions of this molecule merge with the target cell membrane, inducing fusion between virus and cell [9,10].

Fusion is followed by uncoating of the viral core, and deposition of the following core components into the host cell cytoplasm: viral RNA genome, reverse transcriptase (RT), integrase (IN), and virion regulatory proteins. RT begins assembling DNA copies (cDNA) of the HIV genome at a rate proportional to the activation state of the host cell. Since this is a reversal of the usual biological process in which DNA is the template for RNA it is described as reverse transcription. In activated cells, complete synthesis of cDNA occurs within 3 hours; in quiescent cells the process takes somewhat longer. cDNA enters the host cell nucleus as a large molecular complex comprising cDNA, RT and IN. Translocation depends upon specialized transportation molecules that are associated with

pores in the nuclear membrane. The rate of nuclear translocation is also influenced by the activation state of the cell. Once inside the nucleus cDNA inserts into the host cell DNA at sites that are specially prepared by the action of IN. Integrated cDNA is termed 'proviral DNA' and contains the blueprint for creating virus progeny. As the host cell moves through its growth cycle, proviral DNA is transcribed into messenger RNA which is exported into the cytoplasm. There mRNA is translated into new viral structural components, enzymes and genomic elements. Protease (PR) is an essential viral enzyme that is synthesized during this process. Under the influence of PR, viral components associate with host cell membrane and then bud off as immature virions [9,11,12].

PR activity continues after detachment from the host cell; the molecular changes that occur under the influence of this enzyme ensure maturation into a fully infectious virion. The life-cycle of HIV presents a wide variety of potential targets for pharmacological intervention [9].

2.1 Anti-HIV Drug Discovery

Chemistry, pharmacology, microbiology, and biochemistry helped to shape the course of drug discovery and to bring it to a level where new drugs are no longer generated solely by the imagination of chemists but result from a direct dialogue between biologists and chemists. This dialogue, centred on the biochemical mechanisms of drug action, stems from the understanding of biological target structure and function and gives rise to the creation of novel chemical structures [13].

The generation of lead compounds is one of the key rate-determining steps in the drug discovery process. The strategies used to generate novel leads include substrate based (for enzymes), screening and biostructural (using high-resolution structural data of target biomolecules) approaches [14].

The desirable features (criteria) that a novel anti-HIV drug should display are the following [15]:

1) high antiviral activity against wild-type and mutant viruses,
2) high oral bioavailability, allowing once-daily administration,
3) minimal adverse effects, and
4) ease of synthesis and formulation.

The deeper molecular understanding was essential to determine the new optimized molecular targets for drug intervention. Therefore, the interplay between molecular biology, biochemistry, genetics and chemistry have led important additions to the drug discovery rational and to the therapy. In fact, the studies generated in the field of molecular biology have greatly influenced the drug discovery process, allowing that the genetic information could be taken into account so that this information has become a very important player in the drug development [13].

The search for effective drugs against HIV has focused on targeting various critical components of the replication cycle of HIV. One important component in this cycle is the reverse transcriptase enzyme. Indeed, perhaps because of its pivotal role in the life cycle of HIV, it was the target of the first clinically approved anti-retroviral agents [16].

Unless the HIV life cycle is interrupted by specific treatment, the virus infection spreads rapidly throughout the body, which results in the weakness and destruction of the body's immune system. From the analysis of the HIV life cycle, one could conclude that there are several steps that might be interfered with, thus stopping the replication of the virus [8].

The development of effective anti-HIV drugs is difficult due to wide variations in nucleotide and amino acid sequences. The perfect anti-HIV drug chemical should be effective against drug resistance mutation. Understanding the target RT enzyme and its structure, mechanism of drug action and the consequence of drug resistance mutations provide useful information which can be helpful to design more effective NNRTIs. The RT enzyme can undergo change due to mutations that can disturb NNRTI binding.The first two classes of compounds that were identified as NNRTIs were the 1-(2-2-hydroxyethoxymethyl) -6- (phenylthio)thymine (HEPT) and tetrahydroimidazo [4,5,1-jkj] [1,4] benzodiazepin- 2(1H)-one and -thione (TIBO) compounds. The discovery of the TIBO compounds led to the definition of the NNRTI class in the late 1980s when they were unexpectedly found to inhibit RT. This finding initiated researches on mechanism of action for these compounds. The HEPT compounds were described before the TIBO compounds and were originally believed to be NRTIs. Later it was discovered that they shared common mechanism

of action with the TIBO compounds. Both the HEPT and TIBO compounds were first to be identified as highly specific and potent HIV-1 RT inhibitors, not active against other RTs. These compounds do not interrupt the cellular or mitochondrial DNA synthesis. The specificity of the NNRTIs for HIV-1 is considered the hallmark of the NNRTI drug class [17].

The sequence of HIV revealed that it contained a similar protease to murine leukaemia virus. In 1985, Oroszlan published a paper showing, through site-directed mutagenesis, that protease was essential for HIV maturation and was hence a valid target for antiviral therapy. At a time when the medical community was struggling to cope with rapidly developing HIV epidemics, that was extremely welcome news. HIV protease inhibitors now a key component of multidrug HIV treatments are a prime example of structure-based drug design HIV's protease enzymes were validated as a potential drug target in 1985, sparking a race to unravel the enzyme's structure. Structure-based drug design has since become an established drug discovery tool [18].

2.1.1 Classes of currently approved drugs

There are presently more than 25 drugs approved for use against HIV infection and AIDS. They can be divided into six different classes based on their mode of action [19].

2.1.1.1 Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs was the first class of drugs that came into clinical use against HIV in 1987 [20]. They are substrate analogues that act as chain terminators and thereby block reverse transcription performed by HIV RT. NRTIs are administered as pro-drugs that need to be phosphorylated by cellular kinases into their triphosphate form before becoming active. They are unspecific and therefore cause severe side effects. Resistance develops rapidly against all available NRTIs if they are used as monotherapy. Currently, there are seven approved NRTIs: zidovudine (AZT) (1), didanosine (2), zalcitabine (3), stavudine (4), lamivudine (5), abacavir (6), emcitrabine (7) and Tenofovir (8). Their structures are shown in Fig. 1. Tenofovir is an acyclic analogue of adenosine monophosphate. It only requires two intracellular phosphorylations to become active since it already has a phosphanate group attached to it, However, due to poor bioavailability, tenofovir now exists as the ester prodrug tenofovir disoproxil fumarate (TDF) [3,19].

2.1.1.2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs also target the polymerase activity of HIV RT, but through allosteric inhibition. They are highly specific and are therefore better tolerated than NRTIs, causing fewer adverse side effects. Rapid resistance development is a problem also with NRTIs and they are not functional towards HIV-2. There are currently four licensed NNRTIs: nevirapine (9), efavirenz (10), delavirdine (11), and etravirine (12) (Fig. 2).

2.1.1.3. Protease inhibitors (PIs)

PIs inhibit the function of HIV protease, preventing the virus from replicating and making new infective virions. The drugs mimic a peptide substrate in its transition state and were discovered through rational, structure-based drug design.

Once bound to the active site, the inhibtor cannot be cleaved and thereby blocks further catalytic activity. Some PIs inhibit both HIV-1 and HIV-2. This is the largest group of inhibitors with ten licensed drugs: saquinavir (13), ritonavir (14), indinavir (15), nelfinavir (16), atazanavir (17), amprenavir (18), lopinavir (19), fosamprenavir (20), tipranavir (21), and darunavir (22). The structures of these drugs are shown in Fig. 3 [3,19].

2.1.1.4 Integrase inhibitor (INI)

The first, and so far only, approved anti-HIV drug that targets IN is raltegravir (23), approved for clinical use in 2007, Fig. 4. Viral IN has two catalytic functions used in the process of integrating the transcribed viral DNA into the host genome: processing of the 3' ends and a strand transfer reaction, i.e. joining of the viral and cellular DNA. Raltegravir is a specific inhibitor of the rate-limiting strand transfer reaction.

2.1.1.5 Co-receptor inhibitor (CRI)

Maraviroc (24) is a CCR5 antagonist that prevents binding of the HIV virion to the host cell. It was approved in 2007 and is the first drug of its kind, Fig. 5. Maraviroc selectively interferes with the binding of the viral membrane glycoprotein gp120 to the co-receptor CCR5. It is hence only effective against CCR5-tropic HIV strains 23.

Table 1. Summary of the possible HIV targets and interventions [5]

Stage of HIV life cycle	Potential intervention
Binding to target cell	Antibodies to the virus or cell receptor
Early entry to target cell	Drugs that blocks fusion or interfere with retroviral uncoating
Transcription of RNA to DNA by reverse transcriptase	Reverse transcriptase inhibitors
Degradation of viral RNA in the RNA-DNA hybride	Inhibtors of R Nase H activity
Integration of DNA into the host genome	Drugs that inhibit " integrase" function
Expression of viral genes	"Antisense" constructs; inhibtors of tat protein or art/ trs protein
Viral component production and assembly	Myristoylation, glycosylation, and protease inhibtors
Budding of virus	Interferons

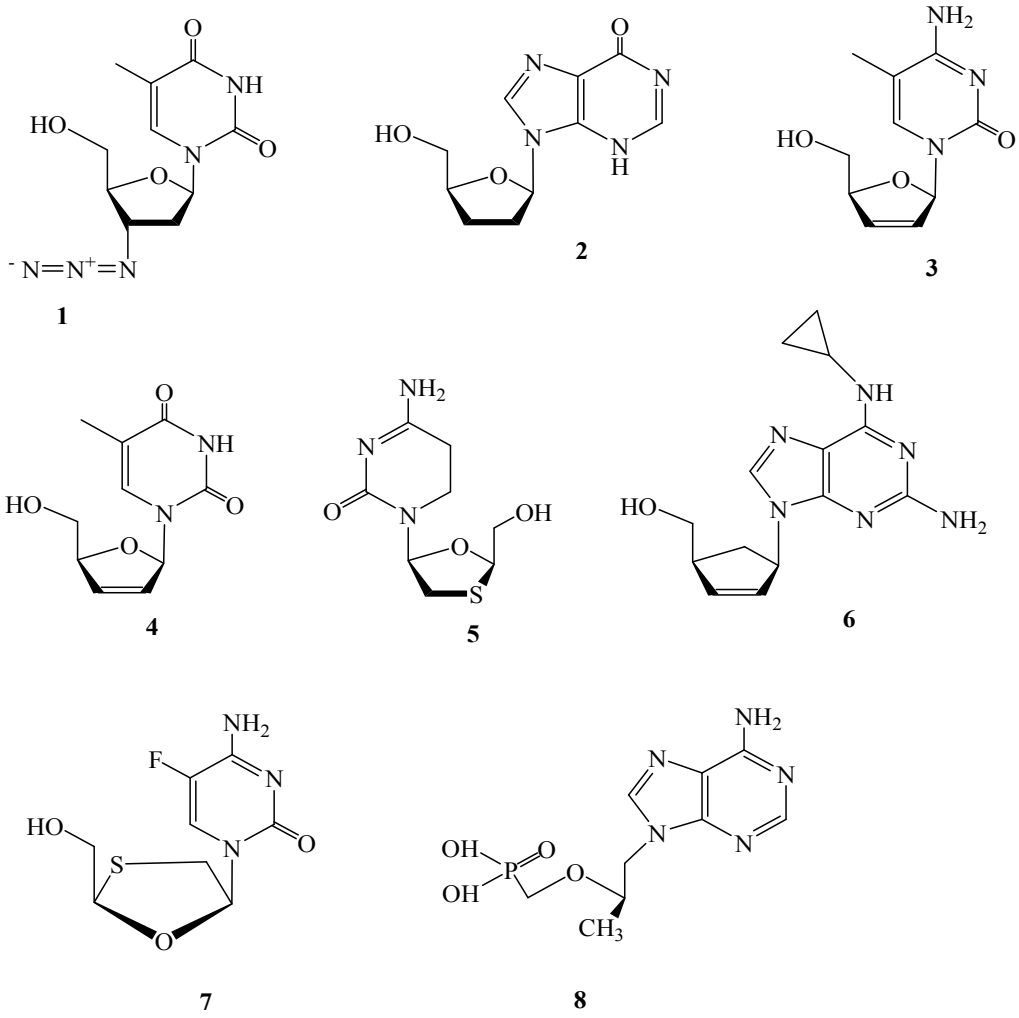

Fig. 1. The chemical structures of the first approved NRTIs

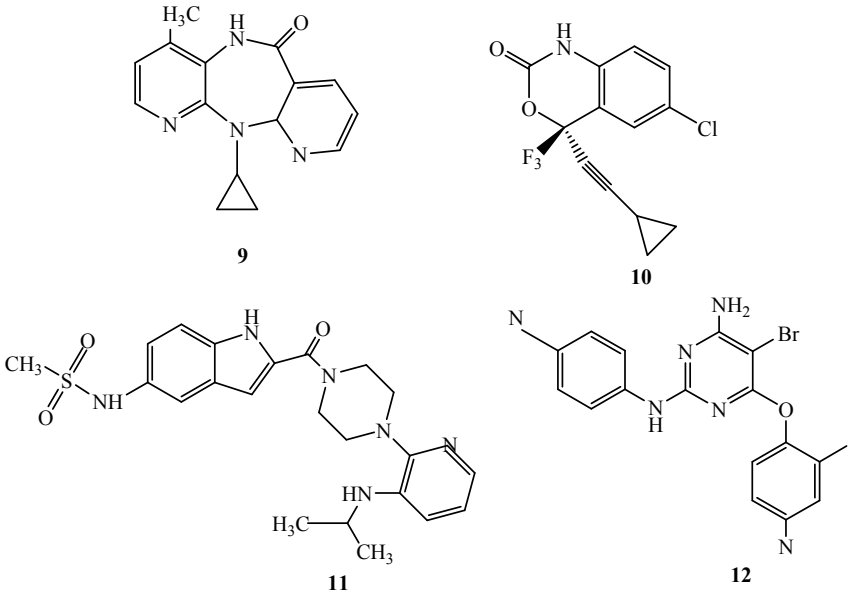

Fig. 2. The chemical structures of the four clinically approved NNRTIs

2.1.1.6 Fusion inhibitor (FI)

Enfuvirtide is a synthetic 36-amino acid peptide that binds to the viral envelope glycoprotein 41. It selectively hinders the anchoring and subsequent fusion of HIV with the host cell membrane. Due to its large size and chemical properties, it has very poor oral bioavailability and must be injected subcutaneously twice daily. It is therefore primarily used in salvation therapy, i.e. when all other therapies have failed [3,21].

2.2 Anti-HIV Drugs Development

Although treatment with antiviral agents has proven to be a highly effective way to improve the health and survival of infected individuals, the epidemic will continue to grow and there is an urgent need to develop new anti-HIV drugs [7].

The first anti-HIV drug, azidothymidine (AZT), was approved in 1987, and more than 30 anti-HIV drugs are currently used for clinical treatment. Although highly active anti-retroviral therapy is effective in controlling the progression of AIDS, the combined use of multiple drugs is greatly hindered by the emergence of drug-resistant HIV strains. More and new anti-HIV drugs are therefore needed for clinical treatment [22].

2.2.1 Combination therapy

Combination therapy for the treatment of HIV is particularly attractive. Attack of virus at different steps in the life cycle should be more effective than attack at a single step. Several combinations of drugs have been tried. Combinations of reverse transcriptase inhibitors and protease inhibitors provide starting reduction in viral levels in AIDS patients. These are the combinations that have reduced viral levels to zero in some patients. The combination of zidovudine and idanosine in particular among patients new to antiretroviral therapy reduced the rate of progression to 39-51 percent compared to patients treated with only zidovudine drug [23].

2.2.2 First generation NNRTIs

After the discovery of HEPT and TIBO, compounds screening methods were used to develop the first NNRTI commonly known as nevirapine. Like HEPT and TIBO, nevirapine blocked viral RT activity by non-competitive inhibition (with respect to dNTP binding). This reinforced the idea that the new class of anti-HIV inhibitors was inhibiting the activity of RT but not at the active site. Several molecular families of NNRTIs have emerged following screening and evolution of many molecules. Three NNRTI compounds of the first generation have been approved by the FDA for treating HIV-1 infection. Nevirapine was approved in 1996, delavirdine in 1997 and efavirenz in 1998. Two of these drugs, nevirapine and efavirenz, are cornerstones of first line HAART while delavirdine is hardly used nowadays. The structure of these three drugs

shows the wide array of rings, substituents, and bonds that allow activity against HIV-1 RT. This diversity demonstrates why so many non-nucleosides have been synthesised but doesn't explain why only three drugs have reached the market. The main problem has been the potency of these compounds to develop resistance [22,24].

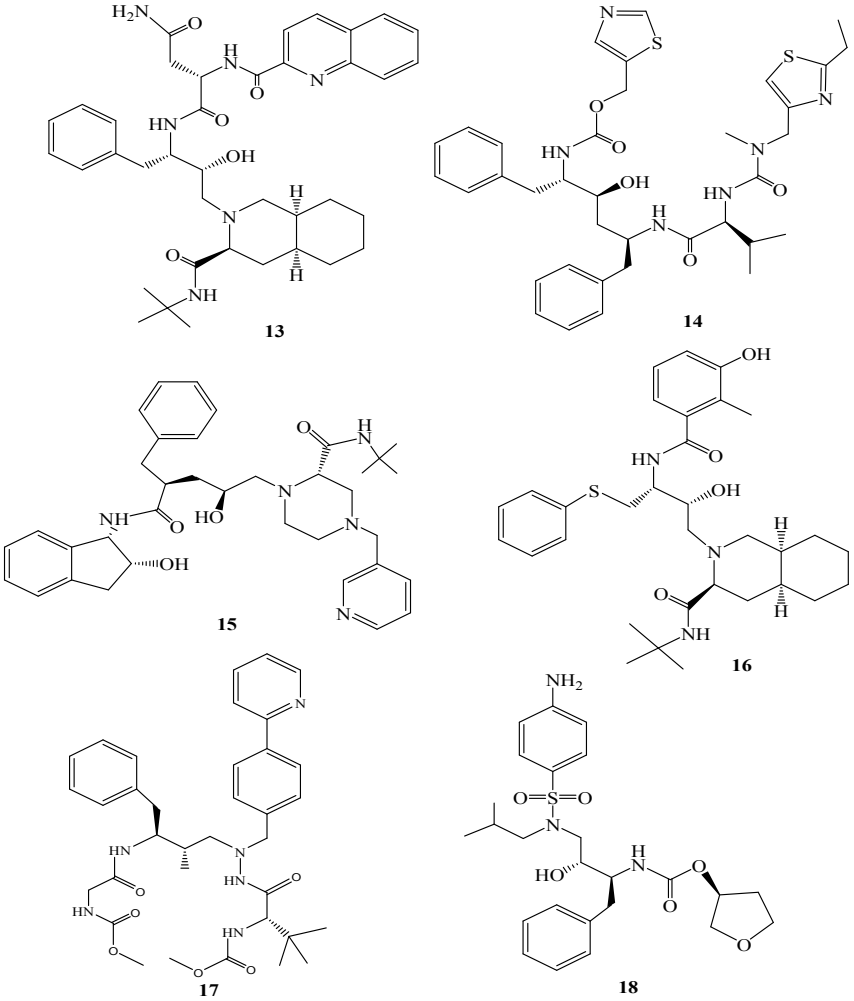

Fig. 3. The chemical structures of the protease inhibitors

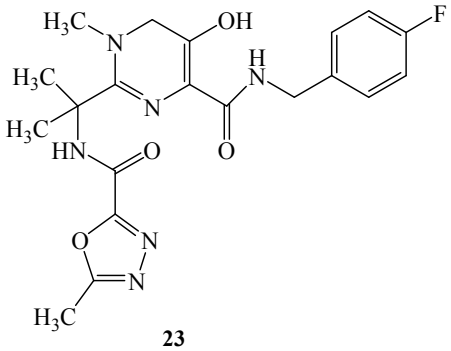

Fig. 4. The chemical structure of the integrase inhibitor raltegravir

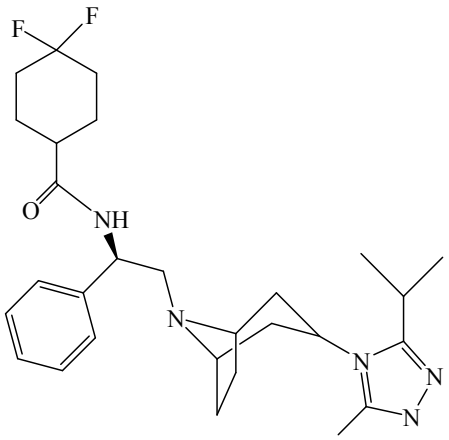

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Fig. 5. The chemical structure of the co-receptor inhibitor maraviroc

Table 2. List of the currently FDA-approved anti-HIV drug combinations

Combination	Components	Date of FDA approval
Combivir	Zidovudine (300 mg),lamivudine (150 mg)	September 27,1997
Trizivir	Abacavir (300 mg), lamivudine (150 mg) zidovudine (300 mg)	November 14, 2000
Epizicom	Abacavir (600 mg), lamivudine (300 mg)	August 2, 2004
Truvada	Tenofovir disoproxil fumarate (300 mg), emtricitabine (200 mg)	August 2, 2004
Atripla	TDF (300 mg), emtricitabine (200 mg), efavirent (600 mg)	July 12, 2006

2.2.2.1 Development from α-APA to ITU

Crystal structure analysis showed that the first generation NNRTIs (for example TIBO, nevirapine and α-APA (25)) bind HIV-1 RT in a "butterfly-like" conformation. These first generation NNRTIs were vulnerable against the common drug-resistance mutations. This triggered the need for finding new and more effective NNRTIs. ITU (imidoylthiourea) (26), a promising series of NNRTIs emerged from α-APA analogs (Fig. 6). The ITU compounds were obtained by extending the linker that binds the aryl side groups of the α-APA. A potent ITU compound, was obtained by an arrangement of the chemical composition of the side groups based on structure-activity relationships (SAR). A crystal structure of the HIV-1/ITU complex demonstrated that ITU compounds are more flexible than α-APA compound. The ITU compounds showed distinct mode of binding where they bound with "horseshoe" or "U" mode. The 2,6-dichlorophenyl part of ITU which corresponds chemically to the wing II 2,6-dibromophenyl part of the α-APA occupied the wing I part in the NNIBP whereas the 4-cyanoanilino part of ITU occupies the wing II position. ITU inhibited HIV-1 and was considerably effective against a number of key NNRTI-resistant mutants like G190A mutation, which caused high-level resistance to loviride (α-APA) and nevirapine. G190A mutation was thought to cause resistance by occupying a part of the binding pocket that would otherwise be filled by the linker part of the butterfly shaped NNRTIs. When compared with nevirapine and loviride which bind in the butterfly shape the ITU derivatives revealed improved activity against certain mutants. The ITU has torsional freedom that enables the conformational alternations of the NNRTI. This torsional freedom could be used by the ITU derivate to bind to a mutated NNIBP and thus compensating for the effects of a resistance mutation. Nevertheless, its potency

against HIV-1 resistant mutants was not adequate for it to be considered as an effective drug candidate [25,26,27].

2.2.2.2 Development from ITU to DATA

Changes in the imidoylthiourea complexes led to the synthesis of a new class of compounds, diaryltriazine (DATA). In these compounds, the thiourea part of the ITU compounds was replaced by a triazine ring. The DATA compounds were more potent than the ITU compounds against common NNRTI resistant mutant strains. Multiple substitutions were made at different positions on all of the three rings and on the linkers connecting the rings. In the pocket, most of the DATA derivatives conformed a horseshoe conformation. The two wings in R106168 (2,6-dichlorobenzyl and 4-cyanoanilino) occupied positions in the pocket similar to that of the two wings of the derivatives of ITU. The central part of the DATA compounds, in which the triazine ring replaced the thiourea group of ITU derivatives. This removed a number of torstional degrees of freedom in the central part while keeping the flexibility between the triazine ring and the wings. Chemical substitution or modification in the three-aromatic-ring backbone of the DATA compounds had substantial effect on the activity. The capability to bind in multible modes made the NNRTIs stronger against drug-resistance mutations. Variability between the inhibitors could be seen when the chemical composition, size of wing I and the two linker groups connecting the rings were altered. The potency of the NNRTIs changed when the triazine nitrogen atoms were substituted with carbons [25,28].

2.2.2.3 Development from DAPY to etravirine

Researchers used multi-disciplinary approach to design NNRTIs with better resistance profile and an increased genetic barrier to the development of resistance. A new class of compounds, diarylpyrimide (DAPY) (27), were discovered with the replacement of the central triazine ring from the DATA compounds, with a pyrimidine. This new class was more effective against drug resistant HIV-1 strains than the corresponding DATA analogs. The replacement enabled substitutions to the CH-group at the 5-position of the central aromatic ring. One of the first DAPY compounds, dapivirine (with R_1= 2,4,6-trimethylanilino, R_2 = R_3 = H and Y = NH) was found to be effective against drug-resistant HIV-1 strains. Systematic chemical substitutions were made at the R_1, R_2, R_3 and Y positions to find new DAPY derivatives. This led to the discovery of etravirine (28) (in Fig. 7) which has a bromine substitution at the 5-position (R_3) of the pyrimidine ring (with R_1 = 2,6-dimethyl-4-cyanoanilino, R_2 = NH_2 and Y = O) [25,29].

2.2.3 Drugs Undergoing Clinical Development

2.2.3.1 Fosdevirine

Fosdevirine (also known as IDX899 and GSK-2248761) (29) is another next generation NNRTI developed by Idenix Pharmaceuticals and ViiV Healthcare. It belongs to the family of 3-phosphoindoles. *In vitro* studies have shown comparable resistance profile to that of the other next generation NNRTIs. On November 3, 2009 the candidate entered phase II clinical trials [24].

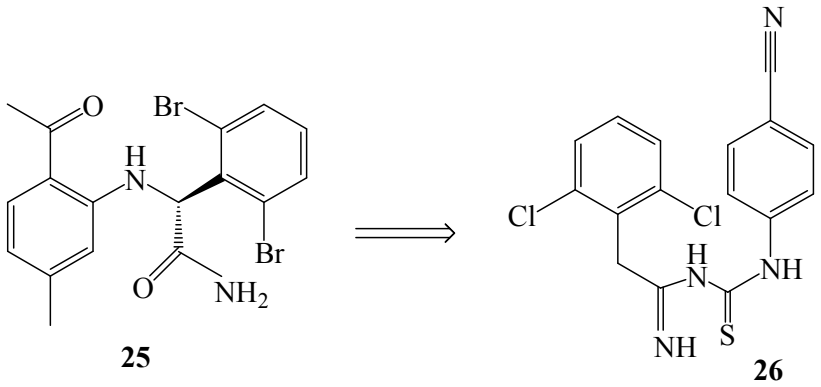
The study of fosdevirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI) was discontinued. In 2011, the US Food and Drug Administration halted all studies of fosdevirine because of seizures that occurred in five participants in a Phase IIb study. It has since been reported that fosdevirine is no longer being developed (Fig. 8) [30].

2.2.3.2 Lersivirine

Lersivirine (30) belongs to the pyrazole family and is another next generation NNRTI in clinical trials developed by the pharmaceutical company ViiV Healthcare. The resistance profile is similar to that of other next generation NNRTIs. In the end of 2009 lersivirine was in phase IIb. In February 2013, ViiV Healthcare announced a stop of the development program investigating lersivirine (Fig. 9) [24,31].

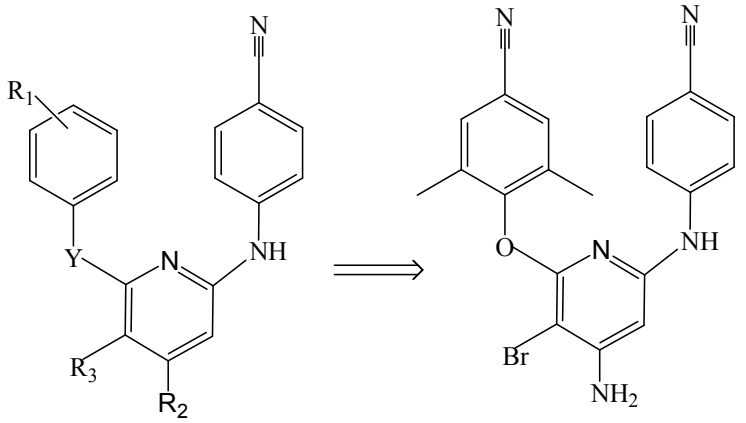
2.2.3.3 Rilpivirine

Rilpivirine (31) is a second-generation non-nucleoside reverse-transcriptase inhibitor (NNRTI) showing in vitro antiretroviral activity up to 20 times greater than efavirenz or nevirapine, the two most common drugs used in first-line regimens in developing countries. Rilpivirine is effective against HIV-1 variants with key NNRTI mutations, and there is a high genetic barrier to the development of rilpivirine resistance (Fig. 10) [32].



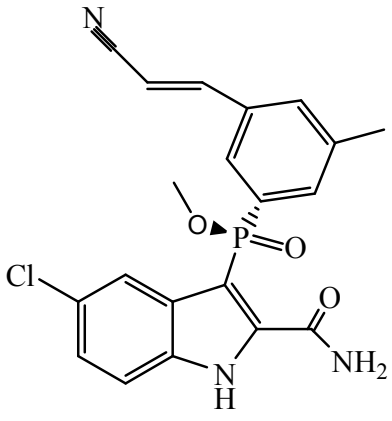
25 26

Fig. 6. The development from α-APA to ITU



27 28

Fig. 7. Chemical substitutions of the DAPY series were made to obtain the highly potent etravirine



29

Fig. 8. The chemical structure of Fosdevirine

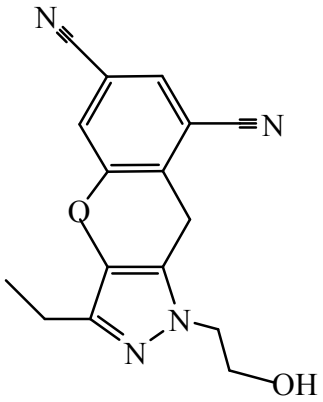


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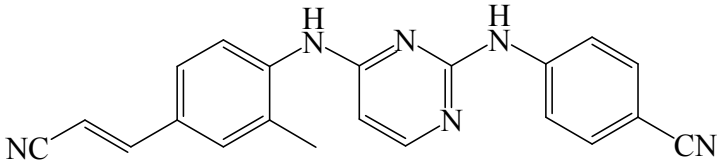
Fig. 9. The chemical structure of Lersivirine



31

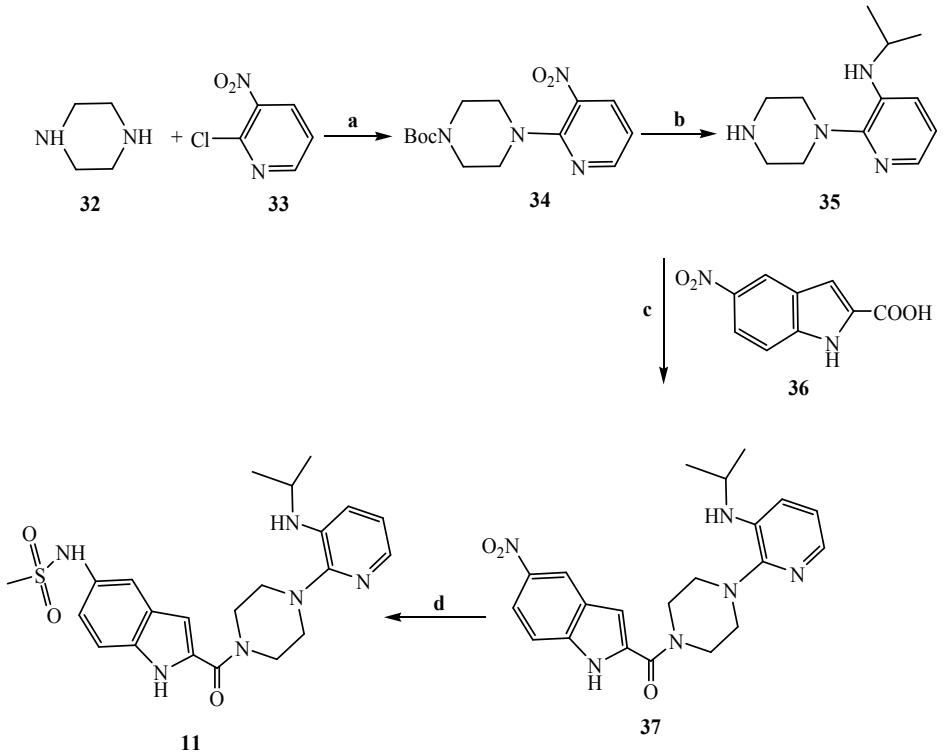
Fig. 10. The chemical structure of rilpivirine

Rilpivirine is a DAPY compound like etravirine and was discovered when further optimization within this family of NNRTIs was conducted. The resistance profile and the genetic barrier to the development of resistance is comparable to etravirine in vitro. The advantage of rilpivirine over etravirine is a better bioavailability and it is easier to formulate than etravirine. Etravirine has required extensive chemical formulation work due to poor solubility and bioavailability. Rilpivirine was undergoing phase III clinical trials in the end of 2009. Rilpivirine was approved by the FDA for HIV therapy in May 2011. A fixed-dose drug combining rilpivirine with emtricitabine and tenofovir was approved by the U.S. Food and Drug Administration in August 2011 under the brand name Complera [24].

2.3 Synthesis of Delavirdine

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are allosteric and non-competitive modulators of RT, one of the key enzymes in the life cycle of HIV-1. They are part of certain multidrug regimens used in the treatment of HIV infection. Delavirdine (Rescriptor) is a specific non-nucleoside inhibitor of HIV-1 reverse transcriptase. It has been approved by the U.S. food and drug administration for its application in the treatment of AIDS and AIDS related opportunistic infections. One can easily discern the presence of two bioactive pharmacophores viz; the indole and the pyridine nucleus in its molecule has been identified recently as an important heterocyclic scaffolds exhibiting impressive anti-HIV activity [33,34].

Synthesis of delavirdine begins with the addition of piperazine (32) to chloropyridine (33) (Scheme 1). The nitro group is reduced and the resultant amine undergoes reductive amination with acetone to provide pyridylpiperazine (35). Coupling of (35) with 6-nitroindole-2-carboxylic acid (36) is accomplished using either 1-ethyl-3-(dimethylamino)propylcarbodiimide (EDC) or 1,10-carbonyldiimidazole (CDI) to give amide (37). The nitro group is reduced under standard palladium on carbon hydrogenation conditions. The resulting amine is then sulfonylated with methanesulfonyl chloride to provide delavirdine, which is then transformed to delavirdine mesylate (11).



Scheme 1. Synthesis of delavirdine

Reagent and condition: a) CH_2Cl_2, $(Boc)_2O$; b) Pd/C, H_2, $NaCNBH_3$, acetone HBr in acetic acid ; c) CDI or EDC; d) Pd/C, H_2, CH_3SO_2Cl, pyr, CH_2Cl_2, CH_3SO_3H

Delavirdine mesylate is given orally at doses of two 200-mg tablets, three times a day. The half-life of delavirdine mesylate is approximately 6 hs. Severe, life-threatening skin reactions have been associated with the use of delavirdine. Skin rashes appear in about 25% of patients. It has demonstrated an IC50 of 0.26 mM against recombinant reverse transcriptase; at 3mM, it halted the spread of virus in T-4 cells and blocked replication of primary HIV-1 isolates in peripheral blood lymphocytes, including zidovudine-resistant variants. Kinetic analysis of delavirdine interaction with reverse transcriptase indicated that it was a mixed-type inhibitor and that it probably impairs the catalytic process subsequent to substrate binding. As its efficacy is lower than other NNRTIs therefore, U.S. Department of Health and Human Services has recommended its use not as a part of initial therapy but in combination with other drugs [34,35].

3. CONCLUSION

The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). This virus is characterized by association with diseases of immune-suppression. HIV has a capacity to hide itself, a high proliferation rate and an extraordinarily high inherent mutation rate. Thus, the virus is capable of quickly adapting to new conditions. This adds to the difficulties of drug development against HIV. Viruses are totally dependent on living cells to survive as they utilize the host cell's own replication processes, in order to reproduce themselves. Binding and fusion, reverse transcription, integration, transcription, assembly and budding are the major steps of the HIV life cycle. HIV infects T cells that carry the CD4 antigen on their surface. The life-cycle of HIV reveals a wide variety of potential targets for pharmacological intervention. Unless the HIV life cycle is interrupted by specific treatment, the virus infection spreads rapidly throughout the body; consequently, the body's immune system is weakened and destroyed.

The generation of novel compounds is one of the key rate-determining steps in the drug discovery process. The search for effective drugs against HIV has focused on targeting various critical

components of the replication cycle of HIV. A polymerase (reverse transcriptase, RT), a protease and integrase are the essential viral enzymes in the cycle.

Depending on the target within the HIV replicative cycle they interact with, anti-HIV compounds are categorized into six groups. These are: nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), cell entry inhibitors or fusion inhibitors (FIs), co-receptor inhibitors (CRIs) and integrase inhibitors (INIs).

The development of effective anti-HIV drugs is difficult due to wide variations in nucleotide and amino acid sequences. The perfect anti-HIV drug chemical should be effective against drug resistance mutation. The development of anti-HIV drug is carried out by bringing a change in the structure of the previously discovered compound and this in turn leads to a drug with higher resistance profile. The synthesis of delavirdine employs the use of heterocyclic rings like substituted pyridine and indole.

4. RECOMMENDATION

Based on results of some researches and reviews, the following recommendations were suggested:

- ✓ Most of the studies focus on improving previously discovered compounds, thus there is a need to conduct a research on synthesis novel compound.
- ✓ There are only few approved drugs that targeted on protease, integrase and co-receptors. Therefore, further studies are required to find other drugs for these targets.
- ✓ Unlike other HIV life cycle stages, there is no sufficient drugs that interrupt the stages of expression of viral genes and viral component production. Hence, it is necessary to find out these drugs.
- ✓ All the anti-HIV drugs inhibit or interrupt the life cycle; hence there is a need to carry out a research to find the drugs that eliminate the virus from the body.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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