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CURRENT INNOVATION IN ANTI-HIV DRUG DISCOVERY AND PRODUCT DEVELOPMENT: A REVIEW

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Abstract:

Rapid development of multidrug-resistant HIV strains, poor bioavailability, and cumulative toxicities have hampered the early effectiveness of combinatorial antiretroviral therapy (cART) in the treatment of HIV infection, necessitating the development of alternative antiretroviral drug discovery strategies and additional therapeutic agents with novel action modes or targets. From this standpoint, we first evaluate current antiretroviral medication discovery and optimization methodologies, using cases from the recent literature as examples. The advent of the substrate envelope concept as a new technique for overcoming HIV drug resistance is highlighted, as is the discovery of phosphate ester-based prodrugs as a means of improving HIV inhibitors' water solubility. Present review focus on HIV Life Cycle, Anti-HIV Drug Discovery, Classes of currently approved drugs, Summary of the possible HIV targets and interventions, Anti-HIV Drugs Development, Perspectives that could inspire future anti-HIV drug discovery.

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INTRODUCTION:

Human immunodeficiency virus type 1 (HIV-1) is the main causative agent of acquired immunodeficiency syndrome (AIDS), which remains a serious public health problem throughout the world. At present, about thirty drugs in five main classes have been approved for the treatment of HIV/AIDS. These drugs target different steps of the viral life cycle:

I. Viral entry (e.g. coreceptor antagonists and fusion inhibitors)
II. Reverse transcription (reverse transcriptase (RT) inhibitors)
III. Integration (integrase (IN) inhibitors)
IV. Viral maturation (protease (PR) inhibitors).[1]

Powerful combinatorial antiretroviral therapy (cART, a combination of anti-HIV drugs targeting different steps in the life cycle of the virus) has had considerable success in controlling HIV infection. However, there are still two key issues: firstly, the emergence of extensively cross-resistant strains of HIV-1 (partly because of poor compliance), and secondly, the adverse effects (poor tolerability, drug-drug interactions, toxicities) of long-term use of these drug regimens, leading to poor patient compliance (namely, failure of patients to adhere to the drug regimen). [2] Thus, there is an urgent need for new anti-HIV drug candidates with increased potency, novel targets, improved pharmacokinetic properties, and reduced side effects.

The traditional approach of random screening and subsequent optimization of lead compounds by systematic organic synthesis is highly resource- and time- consuming. Thus, more efficient and faster strategies that shorten and facilitate the discovery process would be extremely beneficial. Indeed, the discovery of anti-HIV agents is moving on from trial-and-error approaches to sophisticated methodologies. In recent years, several strategies have been employed to discover novel anti-HIV agents with novel scaffolds and better resistance profiles, including fragment-based screening, privileged fragment-based reconstruction, dynamic ligation screening (DLS)-based drug discovery, rapid diversity-oriented synthesis combined with in-situ screening, and hierarchical multiple-filter database searching.

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 nonhuman 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 [4].

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 [5]

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 [6]

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 [7]

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 [8]

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]

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 [10]

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 [11]

The desirable features (criteria) that a novel antiHIV drug should display are the following [12]

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.

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 antiretroviral agents [13]

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.

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-(2-2hydroxyethoxymethyl) -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 [14]

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 structurebased 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 [15]

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 [16]

Nucleoside reverse transcriptase inhibitors:
(NRTIs) NRTIs was the first class of drugs that came into clinical use against HIV in 1987 [17] 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) , didanosine, zalcitabine , stavudine , lamivudine , abacavir , emcitrabine and Tenofovir . 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) .

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 , efavirenz , delavirdine and etravirine.

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 , ritonavir , indinavir , nelfinavir , atazanavir, amprenavir , lopinavir (, fosamprenavir , tipranavir , and darunavir.

Integrase inhibitor (INI):
The first, and so far only, approved anti-HIV drug that targets IN is raltegravir , approved for clinical use in 2007,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.

Co-receptor inhibitor (CRI):
Maraviroc 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 [18].

Table 1: Summary of the possible HIV targets and interventions

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

Fusion inhibitor (FI)
Enfuvirtide is a synthetic 36-amino acid peptide that binds to the viral envelope glycoprotein . 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]

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 antiHIV 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 drugresistant HIV strains. More and new anti-HIV drugs are therefore needed for clinical treatment

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]

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 nonnucleosides 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

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

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 αAPA 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 2,6dibromophenyl part of the α-APA occupied the wing I part in the NNIBP whereas the 4cyanoanilino 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 (αAPA) 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 [20]

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 drugresistance 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 [20].

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) , 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 5position of the central aromatic ring. One of the first DAPY compounds, dapivirine (with R1= 2,4,6-trimethylanilino, R2 = R3 = H and Y = NH) was found to be effective against drug-resistant HIV-1 strains.

Drugs Undergoing Clinical Development:
Fosdevirine
Fosdevirine (also known as IDX899 and GSK2248761) (29) is another next generation NNRTI developed by Idenix Pharmaceuticals and ViiV Healthcare. It belongs to the family of 3phosphoindoles. In vitro studies have shown comparable resistance profile to that of the other next generation NNRTIs.

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.

Lersivirine:
Lersivirine 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. [20]

Rilpivirine:
Rilpivirine is a second-generation nonnucleoside 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.

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 fixeddose 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.[20]

Perspectives that could inspire future anti-HIV drug discovery:
"Privileged structure"-focused substituents decorating approach
The identification of highly potent compounds by the traditional approach of HTS and chemical optimization of leads is also time-consuming and resource-wasting, and probably the potency of these new agents can't go beyond that of the existing ones [26] "Privileged structure" contains multiple sites in the scaffold suitable for structural modification, which can quickly provide novel chemotypes by modifying the central core structure and/or introducing the branching moieties of the existing active compounds. And as such, "privileged structure"-focused substituents decorating (modifying side chains in the existing potent molecules) has been widely used as a robust approach in anti-HIV medicinal chemistry.[21]

Other advantages of the "privileged structure" include:
(1) they have favorable drug-like characteristics;
(2) they exhibit high practicality and feasibility in chemical preparation, which allows rapid synthesis of large amounts of compounds for biological evaluation [22]

Scaffold hopping:
According to the concept that the pharmacophore elements of bioactive compounds for a specific target are discontinuous in certain chemical space. In medicinal chemistry, the search for different structural scaffolds with similar potency is generally of high interest, for example, to facilitate the discovery of new drugs while minimizing intellectual property overlap [23] As a matter of experience in antiviral drug research field, a potential strategy to overcome drug resistance is the discovery of a novel compound with a different chemotype, because it is

possible that a common single mutation is causing resistance to HIV inhibitors.

Natural-product diversification: molecular hybridization and diversity oriented peripheral optimization:

The diverse three-dimensional shapes, functionalities, stereochemistries as well as various interesting biological activities of natural products (NPs) have always provided medicinal chemists with a reliable source in their search for new drug-like compounds [29] At present, NPs are still being explored as potential anti-HIV agents targeting multiple steps in the the HIV life cycle. The attractive concepts of natural-product hybridization and diversity oriented peripheral modification are becoming popular as robust structural diversification approach to design novel and complex NPs molecules. The advantage of these approaches over others is the inherent bioactivity and the high diversity of the privileged NPs scaffolds [24]

Prodrug: an unfading topic:

Prodrug design has demonstrated to be a powerful structural modification strategy to optimize the pharmacological and physicochemical properties, thus the drugs' aqueous solubility and PK profiles can be improved, and their toxicity can be decreased [31] .As we known, a major drawback for nucleoside/nucleotide-based antiviral therapies lies in the activation pathway into the respective functional nucleotide metabolite(s). Over the past decade, with aim to bypass the rate-limiting first-step phosphorylation and to enhance oral absorption and improve drug efficacy, prodrugs of nucleoside monophosphates, referred to as ProTides have been developed [25]

Exploitation of new compounds with unexplored mechanisms of action: pay special attention to "activity cliff":

There is a continuing need for new drugs in controlling AIDS pandemic, in particular those acting through novel and as yet unexplored mechanisms of action to achieve HIV infection cure . As well known, it's not easy to find new scaffold compounds with unexplored mechanisms of action by whole-cell screening campaigns with a large diverse collection of compounds. In drug discovery, it is generally accepted that, slight structural differences between two compounds often resulted in substantial differences in potency, a phenomenon that is known as an "activity cliff" in the activity landscape [26]. Therefore, elaborating the initial screening hits via subsequent medicinal chemistry campaigns, such as lead optimization, comprehensive SAR and mode of action, are still highly desirable to enhance the activity and reduce the side effects [27-28].

CONCLUSION:

Rapid development of multidrug-resistant HIV strains, poor bioavailability, and cumulative toxicities have hampered the early effectiveness of combinatorial antiretroviral therapy (cART) in the treatment of HIV infection, necessitating the development of alternative antiretroviral drug discovery strategies and additional therapeutic agents with novel action modes or targets. Present review focus on HIV Life Cycle, Anti-HIV Drug Discovery, Classes of currently approved drugs, Summary of the possible HIV targets and interventions, Anti-HIV Drugs Development, Perspectives that could inspire future anti-HIV drug discovery.

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