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Review Article

# HIV Integrase Inhibitors

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**ABSTRACT:**

HIV infection is incredibly detrimental and fatal to people. Unfortunately, despite recent advancements and medications, it has not yet been completely eradicated. Opportunistic infections are added to the list of disorders in AIDS (Acquired Immune Deficiency Syndrome), an infectious disease that develops as a result of an impaired immune system. In 2021, there were 38.4 million [33.9-43.8 million] persons living with HIV worldwide, up from 26.0 million [22.9-29.7 million] in 2000. The benefits of vastly expanded access to antiretrovirals, which have contributed to decreasing the number of individuals dying from HIV-related causes, can be observed in the persistence of HIV transmission despite declines in incidence. HIV-1 integration (IN), a critical stage in the integration of viral DNA into the host genome, is vital for retroviral replication. Numerous HIV integrase inhibitors have been created since the identification of this pathway, including Raltegravir, Elvitegravir, Dolutegravir, Bictegravir, and Cabotegravir. HIV integrase inhibitors and their synthesis are covered in this review.

**Keywords** *:* AIDS, HIV, integrase inhibitors.

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## 1. INTRODUCTION

In AIDS (Acquired Immune Deficiency Syndrome), an infectious disease brought on by the immune system's dysfunction, opportunistic infections are added to the list of illnesses. AIDS is caused by HIV (Human Immunodeficiency Virus) [1]. Circumstances and trends In 2021, there were 38.4 million (33.9–43.8 million) persons infected with HIV worldwide, up from 26.0 million (22.9–29.7 million) in 2000. The fact that HIV transmission persists despite declines in incidence is a reflection of the advantages of considerably expanded reach to antiretrovirals, which have assisted to minimize the number of people dying owing to HIV-related causes, notably since 2004 when mortality peaked. In Sub-Saharan Africa, where roughly one in every twenty-five individuals (3.4%) and two-thirds of all HIV-positive persons globally live, the situation is still the worst. That amount (23.4-28.6 million)

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increased to 25.6 million in 2021 [2]. The HIV replication cycle offers numerous crucial targets for pharmacological intervention. The N/NtRTIs, for exampleZidovudine and Zalcitabine, and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), for instance Delavirdine andEfavirenz, the Entry- Fusion Inhibitors, such as the CCR5 antagonist Maraviroc, the Integrase Inhibitors, such as Dolutegravir, and lastly the Protease Inhibitors, like Ritonavir [3].

## 2.HIV INTEGRASE

Retroviral replication requires HIV-1 integrase (IN), which is a crucial step in the integration of viral DNA into the host genome. Although it can happen anywhere in the host genome, particular DNA regionsare favored [4]. In long-lived cells, integrated viral DNA is duplicated alongside host DNA during a period of cell divisions and serves as a latent source for the return of elevated viral loads as soon as the treatment is stopped or the environment is conducive. Pre-integration complex (PIC) is a nucleoprotein complex that transports reverse-transcribed viral DNA into the nucleus of the host cell, where it is integrated with the DNA of the host cell. PIC consists of a few viral core proteins as well as host proteins additionally an IN tetramer plus viral DNA.As part of the PIC in the cytoplasm, which is the first stage of the integration process, IN removes the 2 terminal nucleosides (G, T) from the three ends of the long terminal repeat (LTR) domain of reverse transcribed viral DNA. This process, known as 3-processing (3-P), involves the hydrolysis of the phosphodiester bond.When PIC translocates to the infected cell nucleus, the terminal 3'-OH of the viral DNA assaults the host DNA through a process named as strand transfer. Nucleic acid repair enzymes are then activated after the strand transfer process, completely closing the viral and host strands. Integration is viewed as a fascinating therapeutic aim for the development of anti-HIV lead compounds since it is anessential and distinctive phase in the HIV-1 replication cycle and because IN has nohuman counter part [5,6].

## 3.HIV INTEGRASE INHIBITORS

Raltegravir (MK-0518), the first anti-integrase inhibitor developed by Merck, was approved by the US Food and Drug Administration after a successful clinical trial (U.S. FDA). It was discovered that it was metabolized through glucuronidation and is a member of the diketo acidclass of inhibitors [7]. A successful clinical trial was conducted for Raltegravir, Merck's initial anti-integrase inhibitor. Elvitegravir was created as a result of Sato and colleagues' 2006 demonstration that 4-quinolone-3-carboxylic acids can replace diketoacids (GS-9137) [8]. The U.S. FDA granted approval to the Shionogi-ViiV Healthcare-GlaxoSmithKline joint venture's dolutegravir (S/GSK1349572 or GSK572) drug in August 2013. Treatment with the sodium salt of dolutegravir, an organofluorine, monocarboxylic, heterocyclic substance [9]. Another integrase inhibitor by the name of Bictegravir (BIC; GS-9883) was introduced by Gilead Sciences in 2016 and received FDA approval in 2018. A bridging bicyclic ring and a distinctive benzyl moiety make up the distinctivestructure of BIC [10].

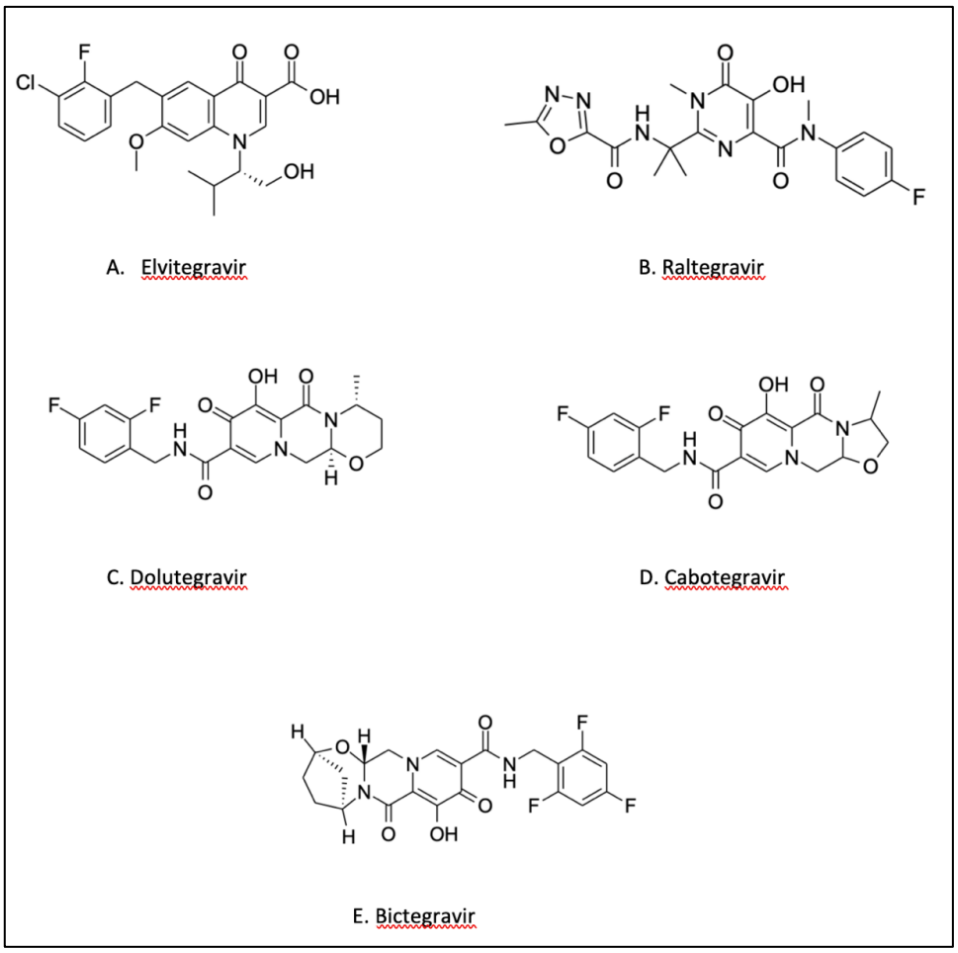


**Fig. 1:** HIV Integrase Inhibitors.

## 4.SYNTHESIS OF HIV INTEGRASE INHIBITORS

### 4.1.Synthesis of Raltegravir

From the commercially accessible 2-amino-2-methylpropanenitrile hydrochloride (2), raltegravir potassium (1) was created over the course of seven synthesis steps. When compound 2's amino group was protected by methylchloroformate in the diisopropylethylamine, (cyano-dimethyl-methyl) carbamic acid methylester was created (3). A crystalline substance known as [1-(N-Hydroxycarbamimidoyl)-1-methyl-ethyl] carbamic acid methylester (4) was created when hydroxyl amine was added to 3. Dimethyl acetylenedicarboxylate (DMAD) was added by Michael to yield 2-(1-methyloxycarbonylamino-1-methyl-ethyl)-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid methyl ester through a subsequent thermal rearrangement (6). N-[(4-fluorophenyl)methyl] was created by reacting 6 with 4-fluorobenzylamine in a triethylamine solution.

1,6-dihydro-5-hydroxy-2[(1-methyl-1-[(methoxy)carbonyl]amino]ethyl carboxamide of -6-oxo-4-pyrimidine (7). In the existence of either magnesium hydroxide, compound 7 was N-methylated toproduce N-[(4-fluorophenyl)methyl]. 1,6-dihydro-5-hydroxy-1-methyl-2-[(1-methyl-1[(methoxy)carbonyl]amino]ethyl] oxo-4-pyrimidine carboxamide, 6 (8). NaOH was used to deprotectthe MOC group in 8 to produce 2-(1-amino-1-methyl-ethyl)-N-[(4-fluorophenyl)methyl]. 1,6-dihydro -1,6-methyl-6-oxo-4-pyrimidine carbo xamide (9). Raltegravir was created by amidating 9 with oxadiazole carbonyl chloride (10) when N-methylmorpholine was present (11). Raltegravir (11) wasconverted into Raltegravir Potassium (1), a crystalline, white substance, by treatment with aqueous KOH in ethanol [11].

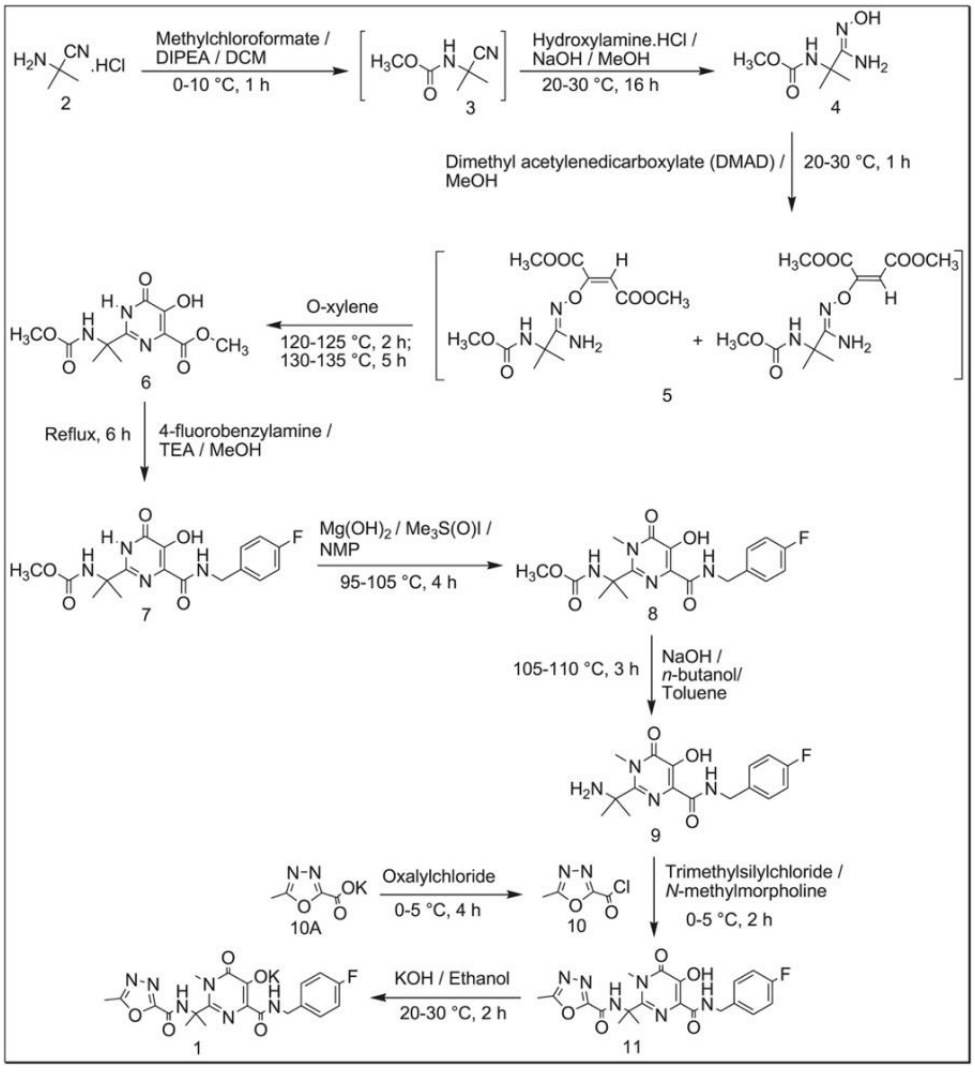


**Fig. 2**: Synthesis of Raltegravir [14]

**4.2.Synthesis of Cabotegravir**

In order to create vinylogous dimethyl amide 13, ketoester 12 was treated to neat DMF-DMA treatment. Following the addition of MeOH, aminoacetaldehyde dimethyl acetal, and concentration to eliminate extra DMF-DMA, vinylogous amide 14 was created.After the mixture was concentrated, pyridone 15 was produced by adding dimethyl oxalate and LiOMe in MeOH. Pyridone-acid 16 was produced as a white solid in an overall 61% yield by selective hydrolysis with LiOH. According to the authors, LiOH had a selectivity of 10:1 for hydrolyzing the target ester, compared to only 3:1 for NaOH and KOH.The way the unfavorable hydrolysis product is eliminated or if the unpleasant monoacid, diacid, or both are the primary by products are not mentioned, though. The original process entailed simultaneously hydrolyzing the methyl ester and the acetal in water, rendering the resulting acid-acetal inert for use in the next step. Hydrolysis utilizing $MeSO_3H$ and HOAc in $CH_3CN$ was developed as a result of research into anhydrous conditions to create acid-aldehyde 17.Without conducting any work-up, (S)-alaninol (10) was incorporated into the mixture and heated to 64 °C for 18.5 hours, resulting in ring closure and the formation of tricycle 18 with 34:1 dr. 18 was crystallized from MeOH with a yield of 74% and a dr of 41:1. After activating the carboxylic acid in DME with CDI, 95% of the reaction's yield was amino 20. at 80 °C and then treated with 2,4-difluorobenzylamine (19). The susceptible aminal moiety, which was difficult to demethylate conventional circumstances utilizing silica/ boron reagents, presented a problem. Clean demethylation was completed using Mg salts, such as $MgCl_2$, $MgBr_2$, and $MgI_2$. This was done under the direction of the cabotegravir mechanism of action, which states that chelation to Mg is essential for integrase inhibition. Cabotegravir was produced with an isolated yield of 93%, but the authors emphasize in the accompanying information that demethylation with LiBr is a morescalablemethod [12].

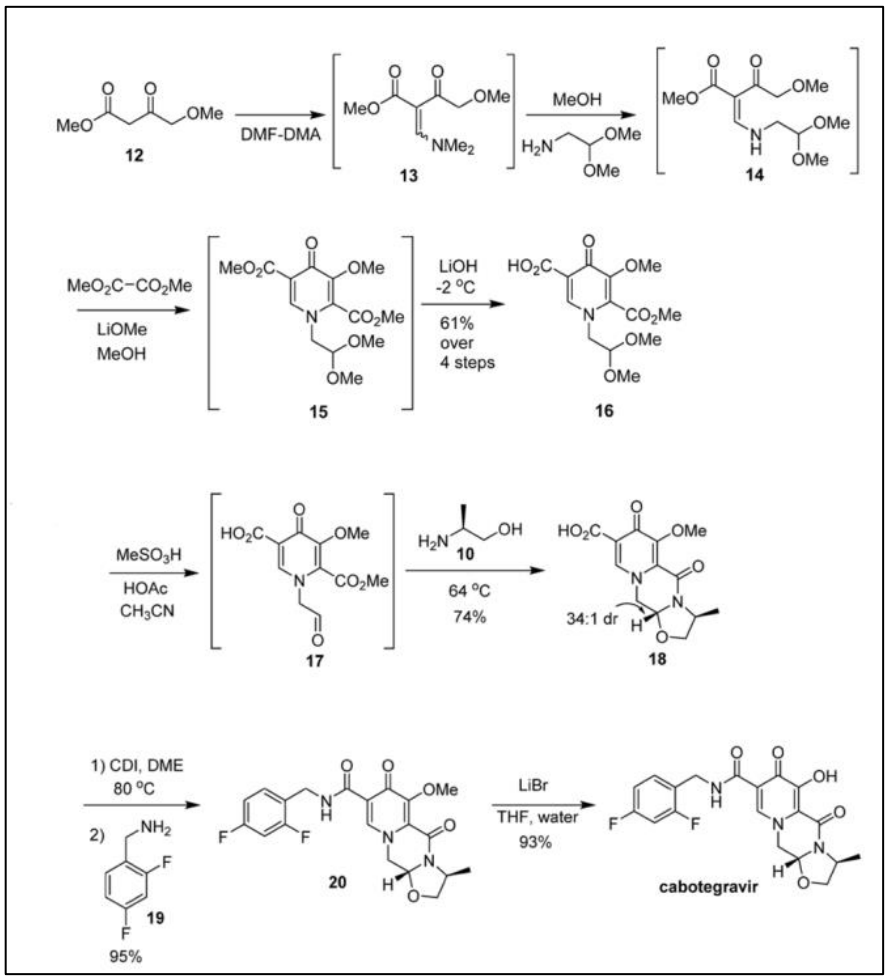


**Fig. 3**: Synthesis of Cabotegravir [14]

### 4.3.Synthesis of Bictegravir

Meldrum's acid is first converted to methoxyacetic acid in MeCN, where it is activated with pivaloyl chloride to produce intermediate 22. 2,4,6-Trifluorobenzyl amine (23) and TFA were added to this solution of 22 in MeCN. The reaction has been worked up and thenextracted by flash chromatography to produce 24 after an 18-hour reaction period at 45–50 °C. After installing the enamine-protected aldehyde 25, the technique then follows chemistry similar to that used to prepare other integrase inhibitors, cyclizing it with diethyl oxalate to produce 26, and so forth. Utilizing either the oxalate/ benzoate salt of (1R,3S)-3-aminocyclopentanol (27) to install the bicyclic ring system, it was possible to produce bicegravir by deprotecting the methyl group together with $MgBr_2$. For any of the phases, noyieldsare listed [13].

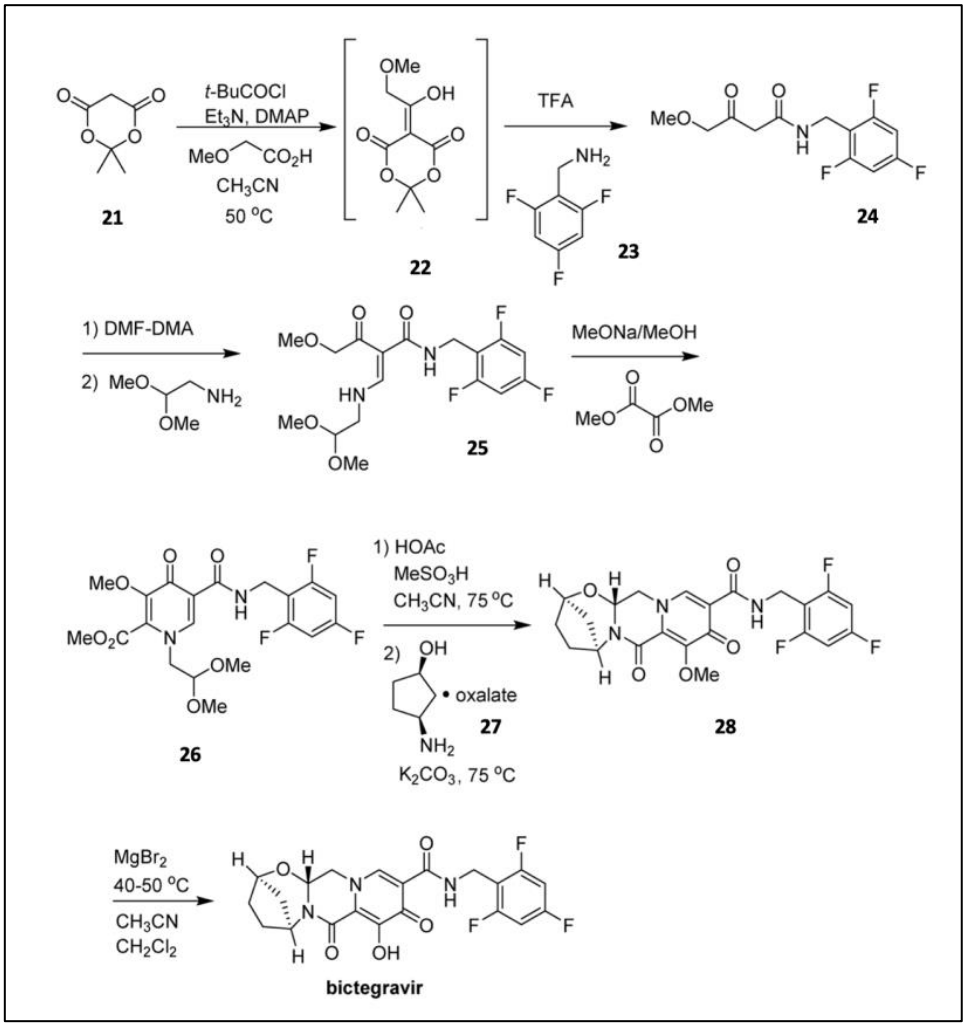


**Fig. 4**: Synthesis of Bictegravir[14]

## 5. CONCLUSIONS

As a result, AIDS has a significant place in drug discovery research due to the disease cannot be completely eradicated. Research on HIV Integrase inhibitors has advanced significantly in recent years as a result of innovations. The current effective use of developed drug molecules in therapy highlights the importance of the possibility of finding undiscovered therapeutic compounds.

### Conflict of Interest

The authors of the article declare that there is no conflict of interest.

### Author Contributions

The authors declare that they have contributed equally to the article.

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