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**INFECTIOUS DISEASES**

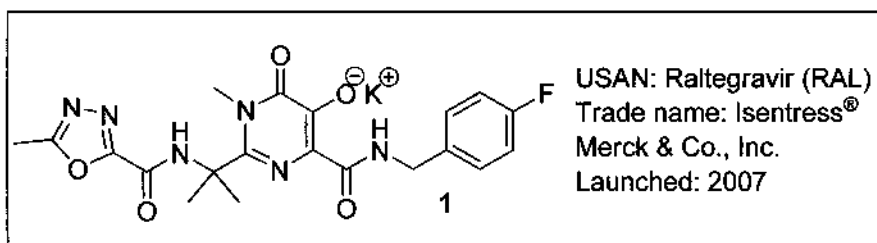
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## Raltegravir (Isentress): The First-in-Class HIV-1 Integrase Inhibitor

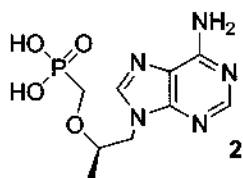
Julianne A. Hunt



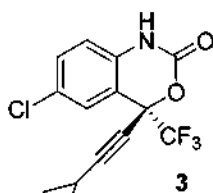
### 1.1 Background

HIV/AIDS is a global pandemic. Nearly three decades of HIV/AIDS research has resulted in the development of more than 20 antiretroviral drugs approved by the U.S. Food and Drug Administration (FDA) for treatment of the disease; combinations of these drugs, known as highly active antiretroviral therapies (HAART), have dramatically decreased morbidity and increased life expectancy.<sup>1</sup> Nevertheless, HIV/AIDS remains a significant cause of morbidity and mortality worldwide. The Joint United Nations Program on HIV/AIDS estimated in 2007 that more than 33 million people lived with the disease worldwide and that AIDS killed more than 2 million people, including 330,000 children. In the United States alone, the Centers for Disease Control and Prevention (CDC) estimated in 2006 that more than one million people were living with HIV infection.<sup>2-4</sup> Although antiretroviral drugs have undeniably changed the lives of many HIV-positive individuals, an unmet medical need clearly exists.

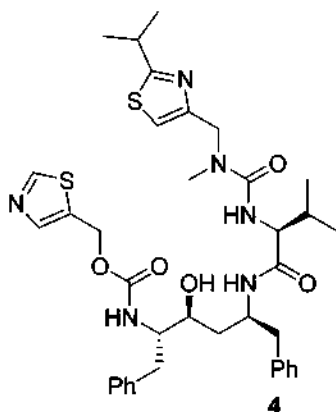
Raltegravir, or Isentress (1), is the first FDA-approved inhibitor of HIV integrase. HIV/AIDS drugs are categorized according to their mode of action as nucleoside and nucleotide reverse transcriptase inhibitors [NRTIs, e.g., tenofovir (2)], nonnucleotide reverse transcriptase inhibitors [NNRTIs, e.g., efavirenz (3)] protease inhibitors [PIs, e.g., ritonavir (4)], fusion inhibitors [e.g., enfuvirtide (5)], entry inhibitors



USAN: Tenofovir (TDF)  
Trade name: Viread®  
Gilead Sciences  
Launched: 2001



USAN: Efavirenz (EFV)  
Trade name: Sustiva®  
Bristol-Myers Squibb  
Launched: 1998

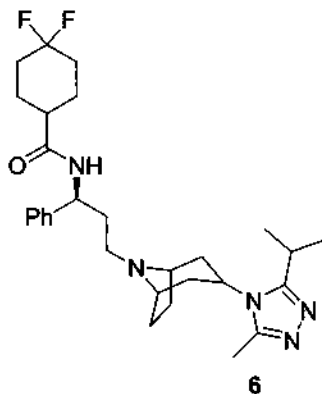


USAN: Ritonavir (RTV)  
Trade name: Norvir®  
Abbott  
Launched: 1996

Ac-YTSLIHSLEESQNQQEKN  
EQELLELDKWASLWNWF-CONH<sub>2</sub>

5

USAN: Enfuvirtide (T20)  
Trade name: Fuzeon®  
Roche  
Launched: 2003



USAN: Maraviroc (MVC)  
Trade name: Selzentry®  
Pfizer  
Launched: 2007

[e.g., the CCR5 antagonist maraviroc (6)], and integrase inhibitors (INSTIs, e.g., raltegravir).

Until recently, all FDA-approved drugs for HIV/AIDS treatment targeted either the viral reverse transcriptase (RT) or protease (PR) enzymes, and treatment guidelines specified that HAART multidrug cocktails should comprise one NNRTI or one PI in combination with two NRTIs.<sup>5</sup> Two of the most significant limitations on the effectiveness of these HAART combinations have been drug-related toxicities and the emergence of resistant viruses.<sup>6</sup> Drugs with novel modes of action—such as viral entry inhibitors and integrase (IN) inhibitors—have been sought to offer antiretroviral treatment-experienced HIV patients who harbor a drug-resistant virus or suffer toxicities with HAART an opportunity to achieve immunologic recovery and virologic suppression. IN inhibitors have been of particular interest to HIV/AIDS researchers because, unlike RT and PR, IN has no human homolog, and thus inhibitors of IN might be better tolerated at high doses.<sup>7</sup>

Raltegravir (1) is the first commercially available antiretroviral agent to target IN; at present, it is the only IN inhibitor approved for clinical use. Launched in 2007, raltegravir was originally indicated for combination therapy with other antiretroviral agents in treatment-experienced adults with evidence of viral replication and multidrug-resistant HIV-1 strains. In July 2009, the FDA approved an expanded indication for raltegravir to include treatment-naïve adult patients, and in December 2009, the U.S. Department of Health and Human Services (DHHS) revised its HIV treatment guidelines to add a raltegravir combination to the preferred regimens for treatment-naïve HIV patients.<sup>5</sup> In this chapter, the pharmacological profile and chemical syntheses of raltegravir will be described in detail.

## 1.2 Pharmacology

The HIV-1 replication cycle involves three key viral enzymes, all of which represent targets for antiretroviral drugs: RT, PR, and IN. RT and PR inhibitors are well represented in the HIV/AIDS treatment armamentarium, but until recently, inhibition of IN had not been successfully exploited in the clinic, despite nearly 20 years of intensive research.<sup>8</sup>

The enzymatic mechanisms of IN have been extensively reviewed.<sup>9</sup> IN catalyzes the insertion of viral genetic material into human DNA through a multistep process that includes 3'-processing, (removal of the terminal dinucleotide from each 3'-end of the viral DNA) and strand transfer (joining of the viral DNA to the host DNA). Both 3'-processing and strand transfer are catalyzed by a triad of acidic residues, D64, D116, and E152, that bind divalent metals such as Mg<sup>2+</sup>. Divalent metals are required for 3'-processing and strand transfer and also for the assembly of the preintegration complex, which allows viral genetic material to cross the host nuclear membrane and access the host genome.

Raltegravir (**1**), like its precursors the 1,3-diketo acids (see Section 1.3), inhibits the strand-transfer activity of IN.<sup>10</sup> The IN-inhibitory activity of raltegravir is most likely the result of functional impairment of the active site arising from chelation of the critical divalent metal cofactors.<sup>11</sup> Raltegravir is both a potent ( $IC_{50} = 10$  nM) and a highly selective inhibitor of integrase activity, found to be essentially inactive ( $IC_{50} > 50$   $\mu$ M) against related enzymes such as hepatitis C virus (HCV) polymerase; HIV RT; HIV RNase-H; and human  $\alpha$ -,  $\beta$ -, and  $\gamma$ -polymerases. In a multiple-cycle cell-based assay (human T-lymphoid cells infected with a laboratory strain of HIV-1 in 50% human serum), raltegravir effectively inhibited ( $IC_{95} = 31$  nM) the replication of HIV-1 infection.<sup>12</sup>

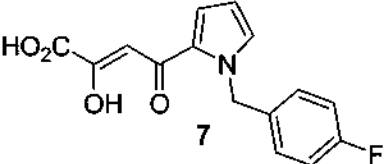
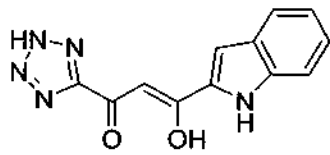
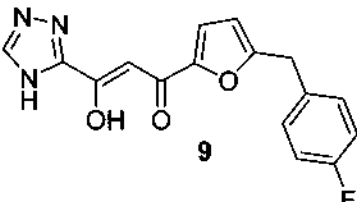
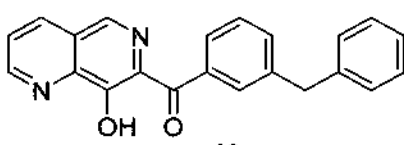
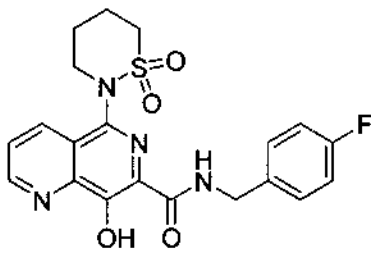
### 1.3 Structure–Activity Relationship (SAR)

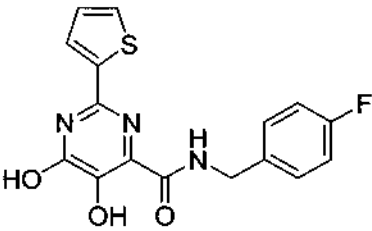
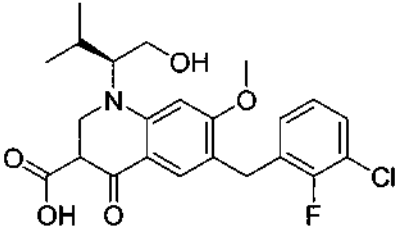
The 4-aryl-2,4-diketobutanoic acid class of IN inhibitors (also known as 1,3-diketo acids, or DKAs) was discovered independently by researchers from Merck and Shionogi, with patents from both groups published in the same year.<sup>13</sup> From a random screen of > 250,000 compounds, the Merck group identified DKAs as the most active IN inhibitors. Compound **7** was the most potent compound found in this screen (Table 1), completely inhibiting HIV-1 infection in a cell-based assay at a concentration of 10  $\mu$ M.<sup>10</sup>

The Shionogi group's first patent<sup>13d</sup> described compounds (e.g., **8**) in which an isosteric tetrazole replaced the carboxylic acid group in the critical but biologically labile DKA pharmacophore. Compound **8**, also known as 5CITEP, inhibited HIV-1 3'-processing as well as strand-transfer activity,<sup>14</sup> and was the first inhibitor co-crystallized with IN.<sup>15</sup> A subsequent patent from the Shionogi group described the systematic modification of the 5CITEP framework to include a variety of heterocyclic replacements for the indole and tetrazole moieties, culminating in the first clinically tested HIV-1 IN inhibitor, compound **9**, also known as S-1360.<sup>16,17</sup> Clinical development of S-1360, undertaken by a Shionogi–GSK joint venture, was halted when the compound failed in efficacy studies in humans (due to formation of an inactive metabolite via reduction at the carbon adjacent to the triazole).<sup>18</sup>

The Merck group's efforts to find a more stable substitute for the DKA pharmacophore resulted in the design of 8-hydroxy-[1,6]naphthyridines such as compound **10**,<sup>19</sup> wherein the keto-enol-acid triad was replaced with a 1,6-naphthyridine ketone bearing a phenolic hydroxyl group. Further refinement of compound **10**—replacement of the naphthyridine phenyl ketone with a 4-fluorobenzyl carboxamide and addition of a six-membered sulfonamide at the 5-position of the naphthyridine core—resulted in compound **11**, the second IN inhibitor to reach the clinic.<sup>20</sup> The discovery of liver toxicity in long-term safety studies of compound **11** in dogs led to the suspension of clinical development<sup>21</sup> of this compound.

Table 1. Activity of DKAs and Related Structures against HIV-1 Integrase

Entry	Compound	HIV-1 Strand Transfer IC <sub>50</sub> (μM)
1	<b>1</b>	0.01
2	 <p style="text-align: center;"><b>7</b></p>	0.08
3	 <p style="text-align: center;"><b>8</b></p>	0.65
4	 <p style="text-align: center;"><b>9</b></p>	0.02
5	 <p style="text-align: center;"><b>10</b></p>	0.04
6	 <p style="text-align: center;"><b>11</b></p>	0.01

7	 <p style="text-align: center;"><b>12</b></p>	0.08
8	 <p style="text-align: center;"><b>13</b></p>	0.007

Concurrent with the Merck group's efforts to find an IN inhibitor that would be successful in the clinic, a separate Merck group working on inhibitors of HCV polymerase discovered that dihydroxypyrimidine carboxamide **12** (which, like the other compounds shown in Table 1, evolved from DKA lead structures) was a potent inhibitor of HIV-1 strand transfer, but completely inactive against HCV polymerase.<sup>22</sup> Modification of the dihydroxypyrimidine core to the corresponding *N*-methylpyrimidinone<sup>23</sup> followed by optimization of the *N*-methylpyrimidinone series with respect to metabolic stability, pharmacokinetic profile, antiviral activity, and genotoxicity led to the identification of raltegravir, the first IN inhibitor to be approved by the FDA.<sup>12</sup>

A second IN inhibitor has reached Phase III clinical trials since the launch of raltegravir. Elvitegravir (**13**) is a dihydroquinolone carboxylic acid; the monoketo acid motif of this series of inhibitors is proposed to mimic the keto-enol-acid triad of the DKA lead structures.<sup>24</sup> Like raltegravir, elvitegravir is a specific inhibitor of HIV-1 strand transfer.<sup>25</sup>

#### 1.4 Pharmacokinetics and Drug Metabolism

The plasma half-life of raltegravir (**1**) in rats was 7.5 h and in dogs was 13 h. Plasma half-life was biphasic in both species, with a short initial ( $\alpha$ ) phase and a prolonged terminal ( $\beta$ ) phase. The major route of metabolism for raltegravir was glucuronidation; the glucuronide was shown to be the conjugate of the hydroxyl group at C5 of the pyrimidinone ring.<sup>12</sup>



In humans, the pharmacokinetics of raltegravir was studied in both healthy HIV-negative subjects and in HIV-infected patients. In healthy HIV-negative subjects, raltegravir was rapidly absorbed; as was seen in preclinical species, concentrations declined from the mean maximum plasma concentration ( $C_{max}$ ) in a biphasic manner, with an apparent half-life of approximately 1 h for the  $\alpha$  phase and an apparent half-life of 7–12 h for the  $\beta$  phase. Raltegravir was generally well tolerated at doses of up to 1600 mg/day for 10 days. The mean plasma concentration of raltegravir at the end of a 12-h dose administration interval exceeded 33 nM (the in vitro  $IC_{95}$  in 50% human serum) after multiple doses  $\geq 100$  mg, supporting twice-daily dosing with doses  $\geq 100$  mg.<sup>26</sup>

In a double-blind, placebo-controlled, dose-ranging study in 35 antiretroviral-naive HIV-infected patients (Protocol 004), subjects were randomized to receive placebo or one of four raltegravir doses (100, 200, 400, or 600 mg) twice daily over 10 days. Although dose proportionality was not observed (possibly due to intersubject variability and the small number of patients), the pharmacokinetic data gathered in this study supported the selection of a 400-mg dose for raltegravir.<sup>27</sup>

While the NRTIs, NNRTIs, and PIs are primarily metabolized in humans via cytochrome P450 (CYP450), raltegravir is neither a substrate nor an inhibitor of CYP450 nor is it an inducer of CYP3A4, indicating that drug–drug interactions with drugs metabolized by CYP450 are unlikely. Instead, raltegravir is primarily metabolized via uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1).<sup>28</sup>

## 1.5 Efficacy and Safety

Raltegravir (**1**) is a potent inhibitor of HIV integrase, originally approved for combination therapy with other antiretroviral agents in treatment-experienced adults with evidence of viral replication and multidrug-resistant HIV-1 strains, and recently (July 2009) approved for combination therapy with other antiretroviral agents in treatment-naive adult patients. Raltegravir is dosed orally twice daily (400 mg); no dose adjustment is required when it is co-administered with other antiretroviral agents.

Phase II clinical trials with raltegravir were conducted in both treatment-naive (Protocol 004) and treatment-experienced (Protocol 005) HIV patients. In Protocol 004, 201 treatment-naive HIV patients received either raltegravir or efavirenz (**3**, the current gold standard for treatment-naive patients) for 48 weeks on a background of tenofovir (**2**) and lamivudine combination therapy. Similar proportions of patients in the raltegravir and efavirenz groups achieved an HIV RNA level of  $< 50$  copies/mL.<sup>29</sup> In Protocol 005, 179 treatment-experienced HIV patients with viral resistance received either raltegravir or placebo in combination with optimized background therapy (OBT) chosen by the investigator. In the raltegravir group, 57–67% of patients achieved an HIV RNA level of  $< 50$  copies/mL, compared with 14% in the placebo group.<sup>30</sup>

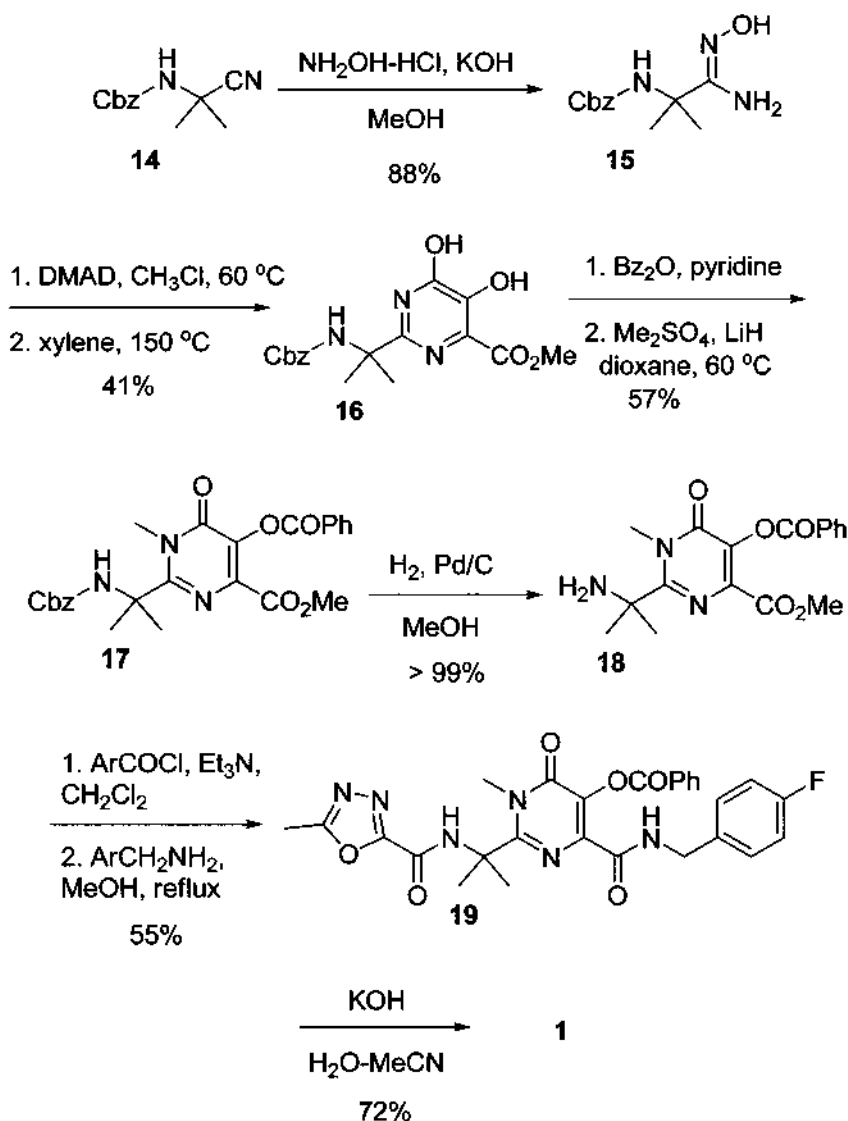
In the two Phase III BENCHMRK clinical trials, 699 treatment-experienced patients with triple-class resistant HIV were randomized to receive either raltegravir (400 mg p.o., b.i.d.) plus OBT or OBT alone. In both trials, patients in the raltegravir group improved both virological (HIV RNA level < 50 copies/mL) and immunological (increased CD4+ cell counts) outcomes compared to patients in the placebo group.<sup>31</sup> In the Phase III STARTMRK study, 563 treatment-naïve patients were randomized to receive either raltegravir (400 mg) or efavirenz (600 mg) in combination with tenofovir and emtricitabine. Analysis of the 48-week results showed that raltegravir-based combination treatment was noninferior to efavirenz-based combination treatment; this study was the basis for the expansion of approved indications for raltegravir to include treatment-naïve patients.<sup>32</sup> Recently, analysis of the 96-week results for STARTMRK confirmed the findings from the 48-week analysis.<sup>33</sup> Finally, 96-week results for Protocol 004 treatment-naïve patients confirmed that the raltegravir group continued to show a suppression of viral replication comparable to that shown by the efavirenz group.<sup>34</sup>

The most commonly reported adverse events of moderate or severe intensity that occurred in > 2% of patients treated with raltegravir were headache, nausea, asthenia/weakness, and fatigue. It is interesting that the STARTMRK study showed that patients on raltegravir-based combination treatment showed significantly less impact on lipid levels than patients on efavirenz-based combination treatment.<sup>32,33</sup>

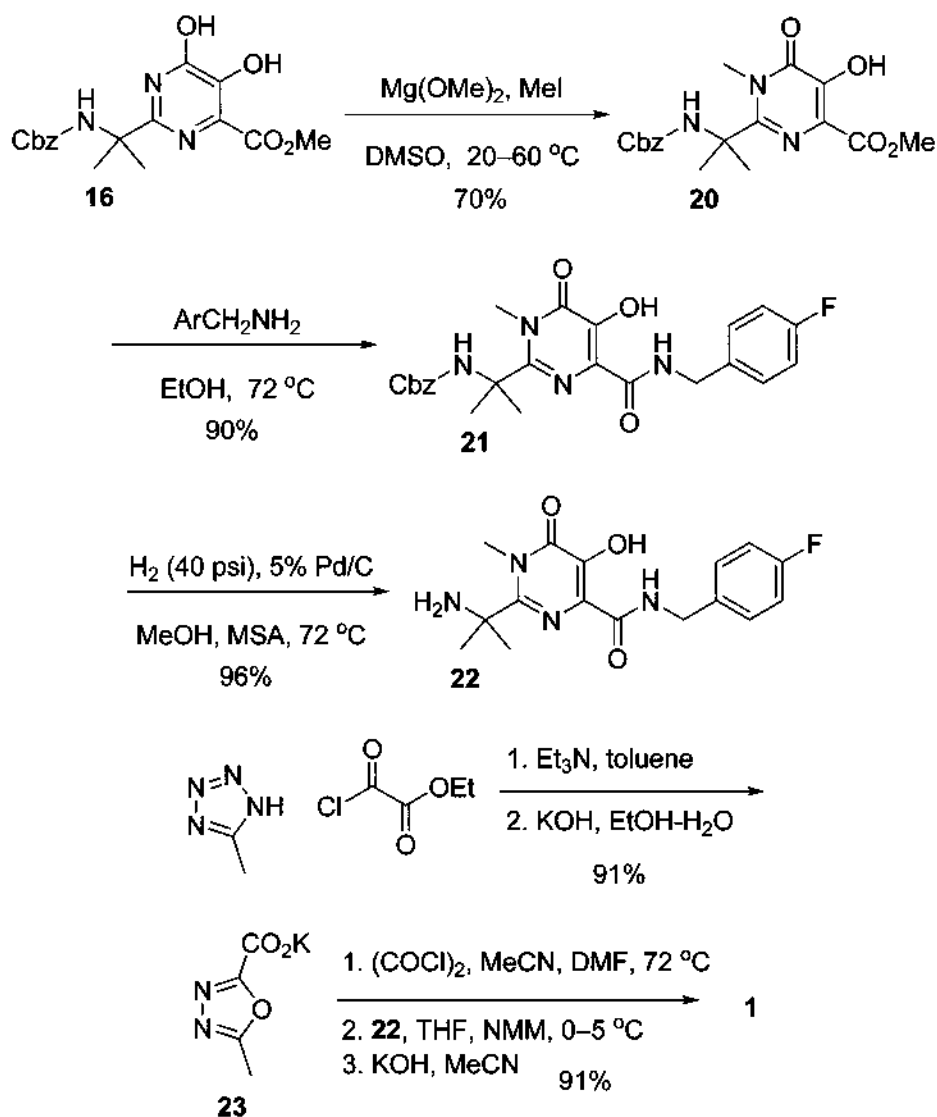
## 1.6 Syntheses

The discovery synthesis of raltegravir,<sup>12</sup> started from nitrile **14**, which was converted to the corresponding amidoxime **15**. Reaction of **15** with dimethylacetylenedicarboxylate provided the dihydroxypyrimidine core (**16**)<sup>35</sup> of raltegravir. Benzoylation followed by methylation provided the *N*-methylpyrimidone **17**, with the *O*-methylated pyrimidine analog (not shown) as a minor product. The discovery route to many analogs of raltegravir proceeded via subsequent installation of the fluorobenzylamide at C4 of the pyrimidone ring, followed by deprotection and functionalization at the C2 position. However, in the case of raltegravir, the preferred route (due to scalability of the purification process) involved functionalization at the deprotected amine **18** to provide the oxadiazole amide at C2 followed by installation of the fluorobenzylamide at C4 to provide up to 10 g of **19**, the free hydroxyl form of raltegravir. Conversion to the potassium salt with potassium hydroxide provided raltegravir potassium **1**.

The process synthesis of raltegravir<sup>36</sup> followed a convergent approach. Synthesis of the pyrimidone amine **22** started from 2-hydroxy-2-methylpropanenitrile, which was converted to the corresponding aminocyanohydrin with ammonia (30 psi, 10 °C, 97% yield), and then protected with benzylchloroformate to provide Cbz-amine **14** in 88% yield. The process synthesis paralleled the discovery route from **14** through **15** to provide **16**, with a somewhat improved yield (52%) for the dihydroxypyrimidine. Deprotonation of **16** with magnesium methoxide followed by treatment with methyl iodide provided the *N*-methylpyrimidone **20** with < 0.5% of the *O*-methylpyrimidine side product. Installation of the fluorobenzylamide was accomplished by heating in ethanol followed by crystallization to provide **21**, and hydrogenolysis of the Cbz-protected amine



provided amine **22**. Synthesis of the oxadiazole **23** began with the reaction of methyltetrazole with ethyl oxalyl chloride to provide the ethyl oxalyltetrazole intermediate, which rearranged with loss of nitrogen on heating in toluene. The crude ethyl ester was saponified with potassium hydroxide to give the oxadiazole carboxylate salt **23**. Finally, reaction of the acid chloride of **23** (formed using oxalyl chloride) with amine **22** provided the free hydroxyl form of raltegravir, which was converted to raltegravir potassium **1** with potassium hydroxide.



In summary, raltegravir (1), which evolved from the DKA class of HIV integrase strand transfer inhibitors, is the first FDA-approved integrase inhibitor. The drug was originally indicated for combination therapy with other antiretroviral agents in treatment-experienced adults with evidence of viral replication and multidrug-resistant HIV-1 strains, but the FDA recently approved an expanded indication to include treatment-naïve patients, and the DHHS has added a raltegravir combination to the list of preferred regimens for treatment-naïve adult patients. Viral resistance to new HIV/AIDS drugs is inevitable, and, indeed, multiple viral amino acid mutations have been identified that confer resistance to raltegravir,<sup>37</sup> necessitating a continuing search for improved

HIV/AIDS therapies. However, the development of raltegravir, the first member of an entirely new class of drugs that target a viral mechanism not previously exploited in the clinic, has provided physicians and patients a welcome addition to the HIV/AIDS treatment armamentarium.

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