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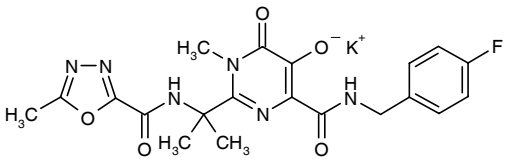
MK-0518

HIV Integrase Inhibitor

MK-518
L-900612 (former code name)
Raltegravir potassium (name under consideration by the USAN Council)

4-[*N*-(4-Fluorobenzyl)carbamoyl]-1-methyl-2-[1-methyl-1-(5-methyl-1,3,4-oxadiazol-2-ylcarboxamido)ethyl]-6-oxo-1,6-dihydropyrimidin-5-olate potassium salt

InChI=1/C20H21FN6O5.K/c1-10-25-26-17(32-10)16(30)24-20(2,3)19-23-13(14(28)18(31)27(19)4)15(29)22-9-11-5-7-12(21)8-6-11;/h5-8,28H,9H2,1-4H3,(H,22,29)(H,24,30);/q;+1/p-1



$C_{20}H_{20}FKN_6O_5$
Mol wt: 482.5069

CAS: 889131-29-7 (potassium salt)

CAS: 871038-72-1 (monopotassium salt)

CAS: 518048-05-0 (free base)

EN: 428015

Abstract

MK-0518 is an HIV integrase inhibitor with potent *in vitro* activity (IC_{95} = 33 nM). Preclinical and clinical studies have demonstrated that MK-0518 was generally very well tolerated, with no serious drug-related adverse events. MK-0518 has shown synergistic activity with all licensed antiretroviral agents. Phase III clinical trials of MK-0518 for the treatment of HIV/AIDS are currently ongoing.

Synthesis

MK-0518 can be prepared as follows:

Acetone cyanohydrin (I) is treated with liquid ammonia in a pressure vessel to produce the aminonitrile (II). After protection of (II) as the benzyl carbamate (III) employing benzyl chloroformate and diisopropyl ethylamine, addition of hydroxylamine to the cyano group leads to the amidoxime (IV). Subsequent condensation of (IV) with dimethyl acetylenedicarboxylate (V), followed by cyclization in hot xylene, gives the pyrimidone (VI), which is methylated to (VII) by means of iodomethane and magnesium methoxide in DMSO. The methyl ester (VII) is then converted to the amide (IX) by treatment with 4-fluorobenzylamine (VIII) under MeOH distilling conditions. Deprotection of (IX) by hydrogenolysis over Pd/C yields the amine (X). The required oxadiazolecarbonyl chloride (XIV) is prepared as follows. Acylation of 5-methyltetrazole (XI) with ethyl oxalyl chloride yields the tetrazolylglyoxylate (XII), which undergoes rearrangement and extrusion of N_2 in hot toluene to generate the oxadiazolecarboxylate (XIII). Subsequent hydrolysis of ester (XIII), followed by chlorination with oxalyl chloride, provides compound (XIV). The pyrimidinone amine (X) is then acylated with acid chloride (XIV) to produce the target amide, which is finally isolated as the crystalline potassium salt MK-0518 (1). Scheme 1.

Background

Current oral anti-HIV agents target the HIV reverse transcriptase and HIV protease enzymes, with different efficacy and safety profiles and dosing regimens. However, drug resistance dramatically reduces the efficacy of these drugs. As one of the three virally encoded enzymes required for HIV-1 replication, the HIV integrase enzyme is considered another potential target for anti-HIV drug development (2-4).

The HIV-1 integrase enzyme, which is highly conserved among clinical isolates, mediates the integration of reverse-transcribed viral DNA into the host cell genome, a necessary step for productive infection by the virus (5, 6). Integration is a multistep process involving binding of integrase to the HIV-1 long terminal repeat (LTR) region, 3'-processing, or the removal of 2 terminal nucleotides from the 3'-ends of double-stranded viral DNA, and strand transfer, or the transfer of viral DNA to human chromosomal DNA (2, 7, 8).

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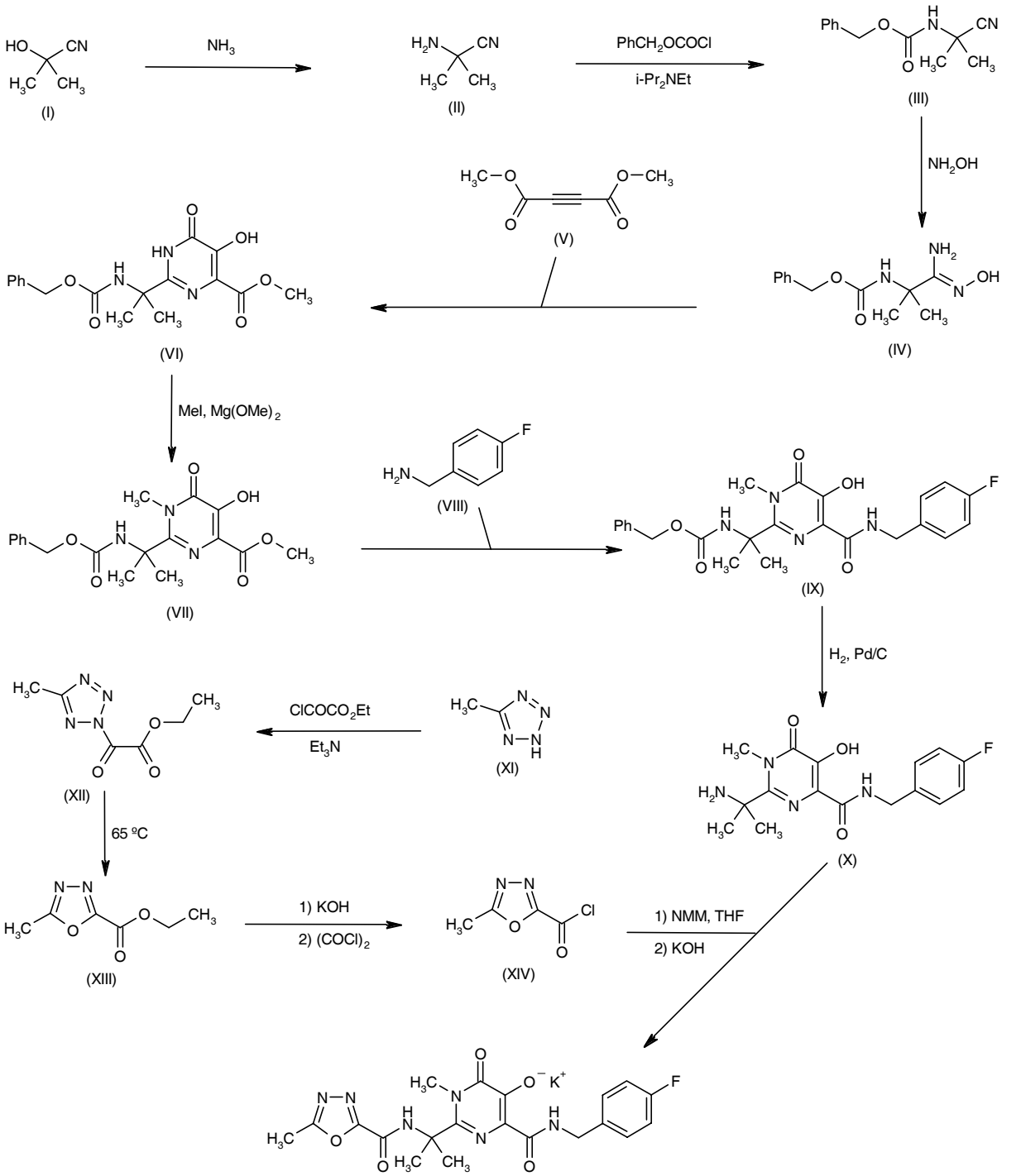
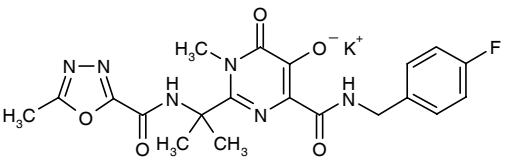
Scheme 1: Synthesis of MK-0518



Merck & Co., one of the first laboratories to screen compounds for their ability to inhibit HIV-1 integrase, discovered a series of diketo acids with potent and selective inhibitory activity against the strand transfer step, and micromolar activity against HIV (9). More potent naphthyridine carboxamides were subsequently synthesized and MK-0518 (MK-518, raltegravir potassium, formerly L-900612) eventually emerged as a clinical candidate and is now in phase III clinical evaluation (2-4). Several other HIV integrase inhibitors are in various stages of clinical development (Table I).

Table I: HIV integrase inhibitors presently in clinical development (from Prous Science Integrity®).

Drug	Source	Phase
1. MK-0518	Merck & Co.	III
2. BMS-707035*	Bristol-Myers Squibb	II
3. GS-9137/JTK-303	Gilead/Japan Tobacco	II
4. S-364735/364735*	Shionogi-GlaxoSmithKline	II
5. GS-9224*	Gilead	IND filed



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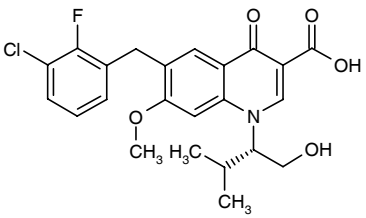

3

*Structure not available

Preclinical Pharmacology

In vitro experiments demonstrated that MK-0518 inhibited the strand transfer activity of purified HIV-1 integrase with an IC_{50} of 2-7 nM and > 1,000-fold selectivity over other phosphoryltransferases tested. MK-0518 demonstrated potent *in vitro* anti-HIV-1 activity (IC_{95} = 19 and 33 nM, respectively, in 10% fetal bovine serum and 50% human serum). The antiviral activity of MK-0518 was attributed to blockade of integrase during infection, as quantitative PCR assays showed that it prevented integration into cellular DNA and enhanced the formation of 2-LTR circular DNA forms, while it did not affect the synthesis of HIV cDNA. When tested in combination with other antiretroviral agents, MK-0518 showed additive or synergistic activity. MK-0518 showed good antiviral activity against a broad panel of HIV isolates, including isolates resistant to other classes of anti-HIV drugs (10).

Pharmacokinetics and Metabolism

Preliminary *in vitro* and *in vivo* pharmacokinetic and metabolic studies in animals predicted a favorable pharmacokinetic profile for MK-0518 in humans and its suitability for twice-daily dosing, which was subsequently confirmed in clinical studies (11, 12).

Pharmacokinetic parameters of MK-0518 were examined in studies carried out in healthy male and female volunteers administered single and multiple doses. Twenty-four healthy males were administered single doses of 10-1600 mg of a lactose formulation of MK-0518 or placebo in the fed or fasted state, 15 other healthy males were administered either a lactose or a poloxamer formulation of the drug at a dose of 400 mg and 8 females were given a dose of 400 mg of the lactose formulation or placebo, and 40 healthy males were administered multiple doses of 100-800 mg MK-0518 lactose formulation or placebo twice daily for 10 days. The results demonstrated that after single doses, MK-0518 was rapidly absorbed (median t_{max} = 0.5-1.3 h) and the drug was eliminated in a biphasic manner with a terminal elimination half-life of 7-12 h. The pharmacokinetic parameters were not affected by moderate- and high-fat meals, and no difference was observed between genders. The poloxamer formulation was associated with lower AUC and C_{max}. After multiple-dose administration, steady state was achieved within 2 days. Results following multiple doses suggested a favorable pharmacokinetic profile for twice-daily dosing (13).

The metabolism of MK-0518 was studied in 8 healthy male volunteers who received a single oral dose (200 mg) of [^{14}C]-labeled drug; and plasma, urine and fecal samples were collected for up to 240 h after dosing. The elimination of MK-0518 and its metabolites was found to be rapid, most of the dose being recovered within 24 h (32% in urine, 51% in feces). UDP-glucuronosyltransferase UGT1A1 was identified as the main isoform responsible for the formation of the major glucuronide metabolite of MK-0518. MK-0518 neither inhibited cytochrome P-450 enzymes nor induced CYP3A, which indicates that it may have limited interactions with drugs metabolized via the cytochrome P-450 system (14).

Clinical Studies

The safety, pharmacokinetics and antiretroviral activity of MK-0518 when used as short-term monotherapy were studied in part 1 of a multicenter, double-blind, randomized phase II study in which 35 antiretroviral therapy (ART)-naïve HIV-1-infected patients with HIV RNA of at least 5000 copies/ml and CD4 count of at least 100 cells/mm^2 received MK-0518 (100, 200, 400 or 600 mg) or placebo twice daily for 10 days. On day 10, the mean decrease from baseline in HIV RNA was 0.2 $\log_{10}$ copies/ml for the placebo group and 1.9, 2.0, 1.7 and 2.2 $\log_{10}$ copies/ml, respectively, for MK-0518 doses of 100, 200, 400 and 600 mg. More than half of the patients in each MK-0518-treated group achieved HIV RNA of < 400 copies/ml by day 10, and the mean trough MK-0518 con-

centrations at each dose exceeded the IC_{95} (33 nM). MK-0518 was generally well tolerated, headache and dizziness being the most common adverse events in all groups (15).

The second phase of the above study has commenced and enrolled 197 patients, whereby these doses of MK-0518 are compared to efavirenz (600 mg once daily), both combined with tenofovir/lamivudine. Preliminary analysis of data at 16 weeks indicated potent antiretroviral activity and generally good safety for both treatments (16).

The effect of MK-0518 on serum lipid levels was also investigated in this trial. Interim results from 184 patients at week 24 revealed that the baseline lipid levels were similar in all treatment groups. In contrast to efavirenz treatment, which markedly increased both serum cholesterol and triglyceride levels from baseline, MK-0518 had little effect on lipid parameters (17).

The safety and efficacy of MK-0518 in HIV-infected patients with documented resistance to 3 classes of ARTs were studied in a multicenter, double-blind, dose-ranging trial. In addition to optimized background therapy (OBT), a total of 178 patients received oral MK-0518 (200, 400 or 600 mg) twice daily or placebo. MK-0518 at all doses demonstrated potent antiviral activity, with a decrease of > 1 log_{10} copies/ml in 77%, 80% and 80%, respectively, *vs.* 18% on placebo, and a decrease to < 50 copies/ml in 65%, 57% and 67%, respectively, *vs.* 14% on placebo at week 24. Generally good tolerance was reported (18).

Because previous research demonstrated that atazanavir (ATV) increased MK-0518 plasma levels, this study was divided into 2 substudies: patients receiving OBT without ATV (substudy A) and patients receiving OBT with ATV (substudy B). At week 8, HIV RNA levels of < 400 copies/ml were obtained in 86%, 86% and 91%, respectively, on 200, 400 and 600 mg MK-0518 compared to 23% on placebo in substudy A, and in 100%, 75% and 100%, respectively, *versus* 33% on placebo in substudy B. At week 8, the percentage of patients with HIV RNA below 50 copies/ml was 63-67% for MK-0518 and 8% for placebo. The most frequent adverse events were diarrhea, nausea, vomiting, fatigue, headache, flushing, pruritus and injection-site reactions, but they were comparable in all groups (19).

Several phase III clinical trials are under way, including studies in combination with OBT in patients failing current antiretroviral therapies (20-22), and in comparison to efavirenz, both in combination with Truvada™ (emtricitabine/tenofovir disoproxil fumarate), in treatment-naïve HIV-infected patients (23).

Drug Interactions

Drug interactions between MK-0518 and various other approved antiretroviral drugs, including ritonavir, efavirenz, ritonavir-boosted tipranavir and tenofovir disoproxil fumarate, were examined in several studies. Results indicated that MK-0518 was generally well tolerated when co-administered with other drugs. Ritonavir did not affect the plasma levels of MK-0518, whereas efavirenz modestly reduced the plasma levels of MK-0518 (24). Tipranavir/ritonavir modestly decreased the mean trough concentrations (C_{12h}) of MK-0518 but did not markedly affect the $AUC_{0\text{-}12h}$ and C_{max} of MK-0518 (25). Tenofovir disoproxil fumarate had no significant effect on the C_{12h} of MK-0518, but modestly increased the $AUC_{0\text{-}12h}$ and C_{max} (26).

To examine the effects of atazanavir (ATV) and ritonavir (RTV) on the pharmacokinetics of MK-0518, an open-label study was carried out in 10 healthy male and female subjects. In period 1, the subjects received 400 mg of MK-0518 alone every 12 h for 4 days. In period 2, the subjects received 400 mg of MK-0518 every 12 h, 300 mg/day of ATV and 100 mg/day of RTV for 10 days. There was no washout interval between the periods. ATV and RTV increased mean MK-0518 C_{12h} by 77%, and $AUC_{0\text{-}12h}$ and C_{max} were also increased by 41% and 24%, respectively (27).

The effect of rifampin on the pharmacokinetic parameters of MK-0518 was also studied in an open-label trial in 10 healthy male and female subjects. MK-0518 (400 mg) alone was administered in period 1, and 600 mg/day rifampin was administered for 15 days with 400 mg MK-0518 administered on day 14 in period 2. In the presence of rifampin, the C_{12h} of MK-0518 was decreased by 61%, $AUC_{0\text{-}last}$ was decreased by 40% and C_{max} was decreased by 38% (28).

The potential pharmacokinetic interaction between MK-0518 and midazolam was examined in another open-label study in 10 healthy male and female subjects who received 2 mg midazolam alone in period 1 and 400 mg MK-0518 every12 h for 14 days with 2 mg midazolam added on day 14 in period 2. MK-0518 did not affect the AUC and C_{max} of midazolam. Because midazolam is primarily metabolized by cytochrome P-450 CYP3A4, this study indicates that MK-0518 is neither an inducer nor an inhibitor of CYP3A4 (29).

Source

Merck & Co., Inc. (US).

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