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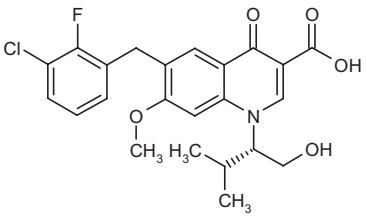
GS-9137

Anti-HIV Agent
HIV Integrase Inhibitor

JTK-303

6-(3-Chloro-2-fluorobenzyl)-1-[1(*S*)-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



$C_{23}H_{23}ClFNO_5$
Mol wt: 447.8836

CAS: 697761-98-1
CAS: 697762-15-5 (as sodium salt)
EN: 414415

Abstract

Significant advances have been made in the development of HIV-1 reverse transcriptase and protease inhibitors for the treatment of HIV infection/AIDS. However, complete suppression of viremia and eliminating the risk of emergence of resistant HIV-1 strains remain critical problems that result in a high rate of treatment failure in HIV-infected individuals. Viral integrase is essential for the replication of HIV-1 and has been identified as a promising target for the development of antiretroviral drugs that interrupt the viral replication cycle. Although considerable research efforts have been made in identifying HIV-1 integrase inhibitors, no such compound has been approved for the treatment of HIV-1. Recently, a series of potential HIV integrase inhibitors derived from quinolone antibiotics were described. The structurally optimized and highly potent monoketo compound GS-9137 (JTK-303) was identified as the most promising candidate, exhibiting potent inhibitory activity against integrase-catalyzed DNA strand transfer and antiviral activity *in vitro*. GS-9137 was shown to be well tolerated in healthy volunteers and HIV-infected patients. Moreover, monotherapy resulted in substantial antiviral activity in infected subjects. The agent is undergoing phase I/II clinical evaluation for the treatment of HIV-1 infection.

Synthesis

GS-9137 can be synthesized by two related ways:

2,4-Difluorobenzoic acid (I) is iodinated by means of *N*-iodosuccinimide in cold concentrated H_2SO_4 to give 2,4-difluoro-5-iodobenzoic acid (II). After conversion of (II) to the corresponding acid chloride (III), condensation with ethyl 3-(dimethylamino)acrylate (IV) affords the benzoyl acrylate (V). Substitution of the dimethylamino group of (V) with (*S*)-valinol (VI), followed by cyclization of the resulting enamine (VII) with K_2CO_3 in DMF, yields the quinolone (VIII) (1-4). The free hydroxyl group of (VIII) is then protected as the carbonate ester (IX) by treatment with methyl chloroformate in the presence of DMAP. The organozinc reagent (XI), prepared by reaction of 3-chloro-2-fluorobenzyl bromide (X) with zinc powder in the presence of trimethylsilyl chloride and 1,2-dibromoethane, is coupled with iodoquinolone (IX) by means of $Pd(PPh_3)_2Cl_2$ to furnish the 6-benzylquinolone derivative (XII). After alkaline hydrolysis of ester (XII), the 7-fluoro group in the deprotected quinolone (XIII) is displaced with sodium methoxide to afford GS-9137 (1, 2). Scheme 1.

In an alternative method, the side-chain hydroxyl group of quinolone (VIII) is protected as the silyl ether (XIV) using *tert*-butyldimethylsilyl chloride and imidazole. Subsequent Negishi coupling of iodoquinolone (XIV) with 3-chloro-2-fluorobenzyl zinc bromide (XI) gives the 6-benzylquinolone (XV), which is deprotected to (XIII) under alkaline hydrolysis conditions. Finally, displacement of the 7-fluoroquinolone (XIII) with methanolic NaOMe provides GS-9137 (3, 4). Scheme 1.

Background

According to UNAIDS, there are currently 40.3 million people living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) worldwide, with 4.9 million new HIV infections and 3.1 million deaths due to HIV/AIDS-related causes reported in 2005. There have been significant advances in the

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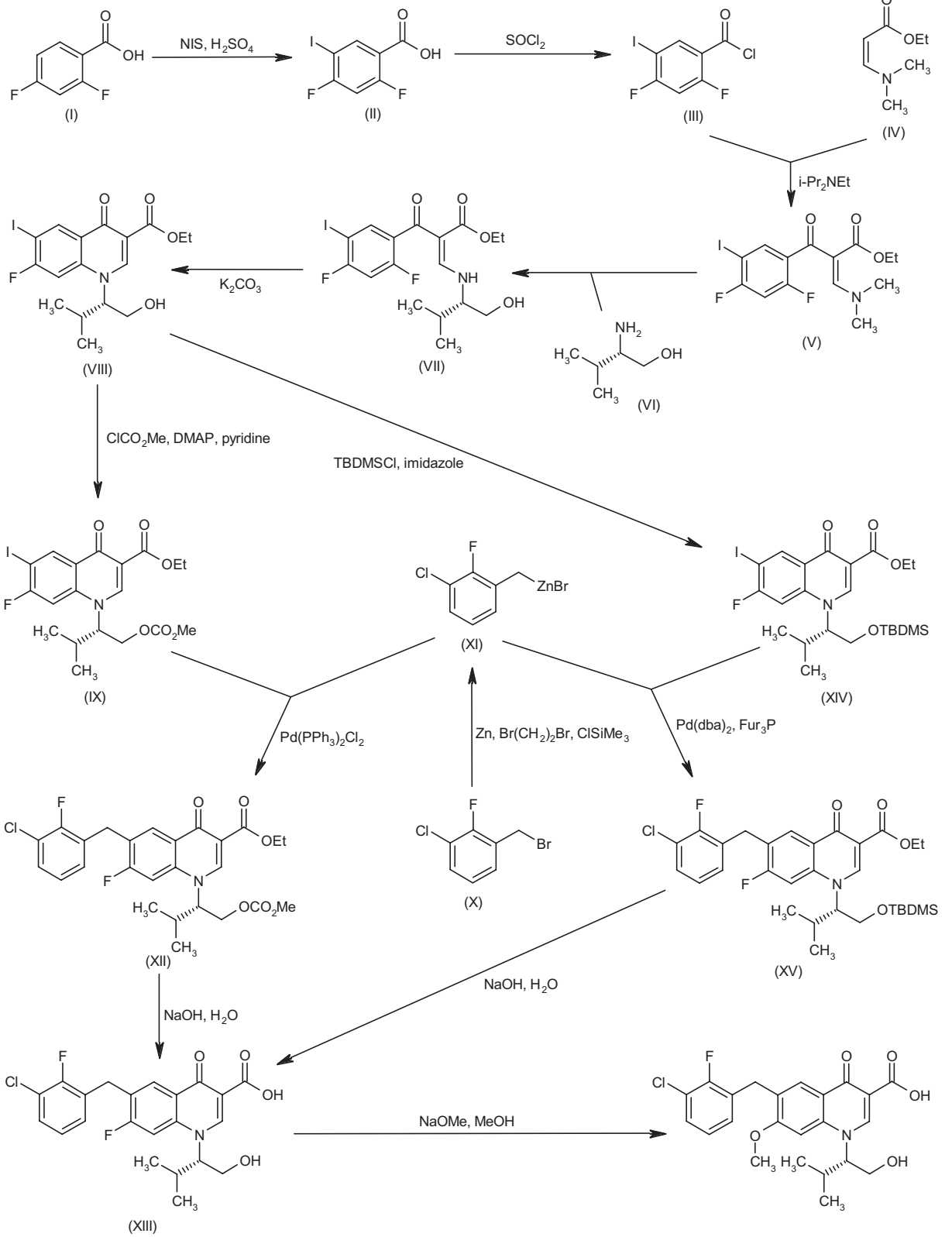
Scheme 1: Synthesis of GS-9137



development of HIV-1 reverse transcriptase and protease inhibitors. However, complete suppression of viremia and elimination of the risk of emergence of resistant HIV-1 strains have not been achieved. The presence of HIV-resistant strains continues to account for more than 70% of all treatment failures in HIV-infected individuals. Researchers therefore continue to search for novel and more effective targets for the development of effective anti-HIV therapies (5).

Viral integrase is essential for the replication of HIV type 1 (HIV-1) and is therefore a promising target for the development of antiretroviral drugs that interrupt the viral replication cycle. HIV-1 integrase catalyzes 3'-processing, which involves the removal of the terminal dinucleotide from each 3'-end of viral DNA. The enzyme then mediates strand transfer, which is the joining of the 3'-end of viral DNA to host DNA. Although research has focused on the development of HIV-1 integrase inhibitors, no such compound has yet been approved for the treatment of HIV-1 infection and, until now, only the diketo class of HIV-1 integrase inhibitors has reached advanced stages of development (5-14). Table I shows HIV-1 integrase inhibitors under active development.

A series of potential anti-HIV therapeutics derived from quinolone antibiotics have been described. The structurally optimized and highly potent monoketo compound GS-9137 (JTK-303) was identified as the most promising candidate and is at present undergoing early clinical evaluation for the treatment of HIV-1 infection (4).

Preclinical Pharmacology

GS-9137 possesses very little antibacterial activity. However, it effectively inhibited integrase-catalyzed DNA strand transfer (IC_{50} = 7.2 ± 2.2 nM), being more potent than compounds from the diketo acid class. In addition, GS-9137 demonstrated marked antiviral activity in an acute HIV-1 infection assay using human T-lymphoid MT-4 cells (EC_{50} = 0.9 ± 0.4 nM), with low cytotoxicity (CC_{50} = 4.0 ± 0.8 μM) (4, 13, 14).

The HIV-1 integrase-inhibitory effects of GS-9137 were investigated in a microtiter plate assay using recombinant HIV-1 integrase (NL4.3) and short DNA oligonucleotides. GS-9137 inhibited strand transfer with an IC_{50} of 8.8 nM, being 3-fold more potent than L-870810. Cell-based experiments revealed that this compound effectively blocked the replication of HIV-1_{IIIB} in human peripheral blood mononuclear cells (PBMCs) in the absence or presence of 50% human serum (EC_{90} = 1.2 and 9.8 nM, respectively), and inhibited the replication of HIV-1 clinical isolates (subtypes A, B, C, D, E, F, G, O) and drug-resistant isolates with EC_{50} values of 0.02-1.26 nM. The compound displayed synergistic activity *in vitro* with lamivudine and lamivudine/zidovudine, and additive activity with zidovudine, tenofovir, tenofovir/lamivudine, efavirenz, indinavir and nelfinavir, in experiments using HIV-1_{IIIB}- infected CEM-SS cells (15).

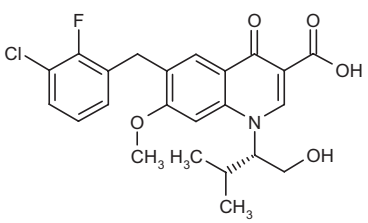
Pharmacokinetics and Metabolism

The pharmacokinetics of single-dose GS-9137 (3 mg/kg p.o.) were examined in nonfasting rats and dogs. Bioavailabilities, total body clearance, $AUC_{0-\infty}$ and $t_{1/2}$ values for rats and dogs were, respectively, 34.1% and 29.6%, 0.5 and 1.0 l/h/kg, 4.5 and 1.9 μM.h and 2.3 and 5.2 h, respectively (15).

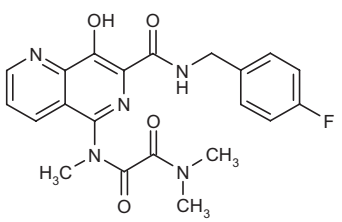
The pharmacokinetics, safety and tolerability of GS-9137 were assessed in a single-blind, randomized, placebo-controlled study. Administration of single escalating doses of the compound (100, 200 or 800 mg or 400 mg plus an additional 400 mg with breakfast after a washout period) to fasting healthy Japanese male volunteers was safe and well tolerated, with no grade 3 or 4 adverse events or significant ECG changes reported at any of the doses tested. C_{max} was achieved at 0.5-4 h postdosing and C_{max} and AUC values increased with dose from 100 to 800 mg. Food significantly increased the C_{max} value by approximately 3-fold as compared to the fasted state. Plasma concentrations of the agent at 12-24 h were superior to protein binding-adjusted EC_{90} concentrations obtained *in vitro* (16).

Table I: HIV integrase inhibitors under active development (from Prous Science Integrity®).

Drug	Source	Phase
1. MK-518*	Merck & Co.	III
2. GS-9137 (JTK-303)	Gilead Sciences/Japan Tobacco	II
3. L-870812	Merck & Co.	I



(**2**)



(**3**)

*Structure not available

Clinical Studies

The antiviral activity and safety of GS-9137 (200, 400 or 800 mg twice daily, 800 mg once daily or 50 mg boosted with 100 mg of ritonavir once daily) were examined in a prospective, randomized, double-blind, placebo-controlled study in 40 HIV-1-infected treatment-naïve and -experienced patients who were not receiving antiretroviral therapy (mean baseline viral load = 4.75 $\log_{10}$ copies/ml; mean CD4 count = 442 cells/μl). All patients were administered GS-9137 with food for 10 days. Treatment was well tolerated and adverse events seen were only grade 1 or 2 in severity, not related to GS-9137 dose and resolved with treatment; no serious adverse events or discontinuations were reported. Substantial and significant antiviral activity was observed with all regimens. Median decreases in HIV-1 RNA from baseline for the respective dose cohorts were 1.48, 2.03, 1.77, 0.96 and 2.03 $\log_{10}$ copies/ml as compared to 0.26 $\log_{10}$ copies/ml for placebo (17, 18).

Ritonavir-boosted GS-9137 is being compared to ritonavir-boosted protease inhibitors in combination with background antiretroviral therapy in a phase II clinical trial in treatment-experienced patients (19).

Sources

Japan Tobacco, Inc. (JP); licensed worldwide (except Japan) to Gilead Sciences, Inc. (US).

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