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MONOGRAPH

CENICRIVIROC MESILATE

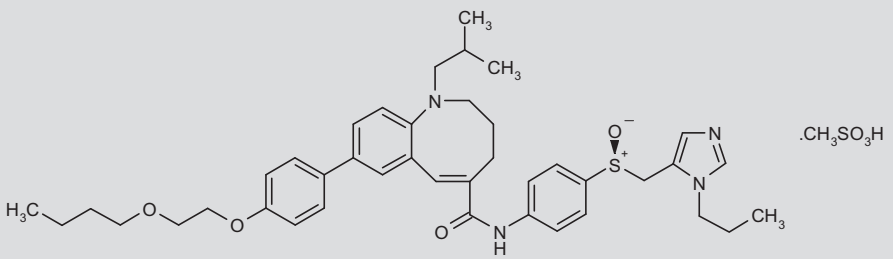
Chemokine CCR2/CCR5 Receptor Antagonist
Anti-HIV Agent

Prop INNM; USAN

TAK-652
TBR-652

(–)-(*S*)-8-[4-(2-Butoxyethoxy)phenyl]-1-isobutyl-*N*-[4-(1-propyl-1*H*-imidazol-5-ylmethylsulfinyl)phenyl]-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide methanesulfonate

InChI: 1S/C41H52N4O4S.CH4O3S/c1-5-7-22-48-23-24-49-38-15-10-32(11-16-38)33-12-19-40-35(25-33)26-34(9-8-21-44(40)28-31(3)4)41(46)43-36-13-17-39(18-14-36)50(47)29-37-27-42-30-45(37)20-6-2;1-5(2,3)4/h10-19,25-27,30-31H,5-9,20-24,28-29H2,1-4H3,(H,43,46);1H3,(H,2,3,4)/b34-26+;/t50-;/m0./s1



$C_{42}H_{56}N_4O_7S_2$

Mol wt: 793.047

CAS: 497223-28-6

CAS: 497223-21-9 (free base, no stereochemistry)

CAS: 497223-25-3 (free base)

CAS: 497223-27-5 (oxalate salt)

EN: 336260

SUMMARY

The prognosis for patients suffering from HIV-1 infection has improved since the introduction of highly active antiretroviral therapy. However, as the emergence of multidrug-resistant mutants often results in the failure of therapy, it seems mandatory to discover anti-HIV-1 agents with a novel mode of action. In this context, the essential steps of HIV-1 entry in the host cell offer several potential new targets for antiviral agents. In fact, an attempt to suppress R5 HIV-1 replication may be able to block viral transmission and delay disease progression. Therefore, chemokine CCR5 receptor antagonists have attracted a great deal of attention as novel anti-HIV-1 candidates. Cenicriviroc mesilate (TBR-652) is a highly potent and selective inhibitor of HIV-1 replication. In addition, cenicriviroc mesilate has the unique property of being a dual antagonist of the chemokine receptors CCR5, a coreceptor required for HIV infection, and CCR2, a coreceptor involved in metabolic and cardiovascular diseases. Ceniciriviroc mesilate is orally bioavailable and has a favorable pharmacokinetic profile in humans, and pharmacokinetic results support the feasibility of once-daily administration. It is also generally well tolerated, with no dose-limiting adverse events.

SYNTHESIS*

Cenicriviroc mesilate can be prepared by two related strategies:

In one strategy, chlorination of benzazocine-5-carboxylic acid derivative (I) with $(COCl)_2$ (1, 2) or $SOCl_2$ in THF (3) yields the corresponding acyl chloride (II) (1-3), which then couples with *S*-Cbz-4-thioaniline (III) in the presence of Et_3N in THF to afford, after hydrolysis of the Cbz group with NaOH in MeOH, the corresponding *N*-(4-sulfanylphenyl)amide (IV). Subsequent *S*-alkylation of thiol (IV) with

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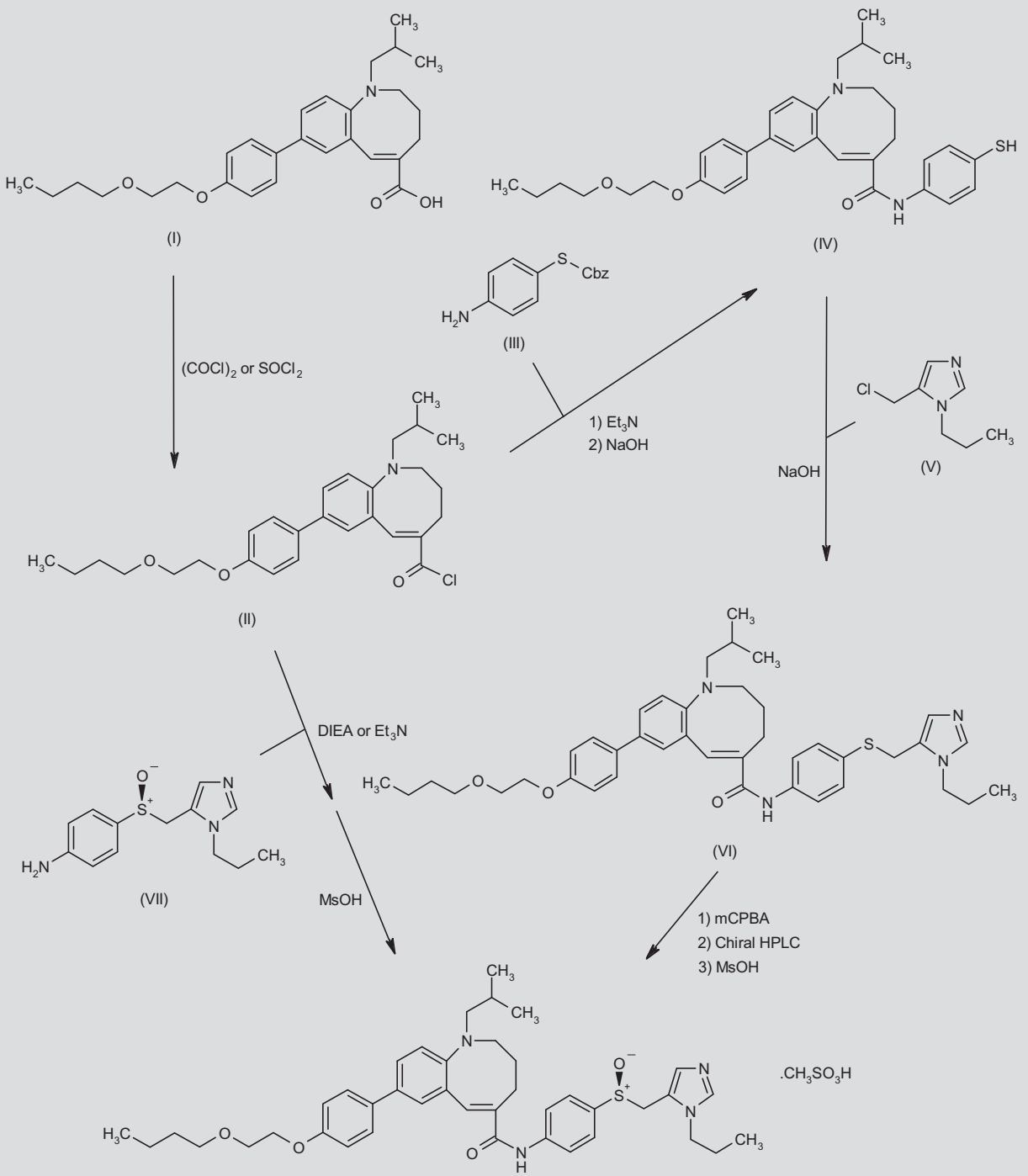
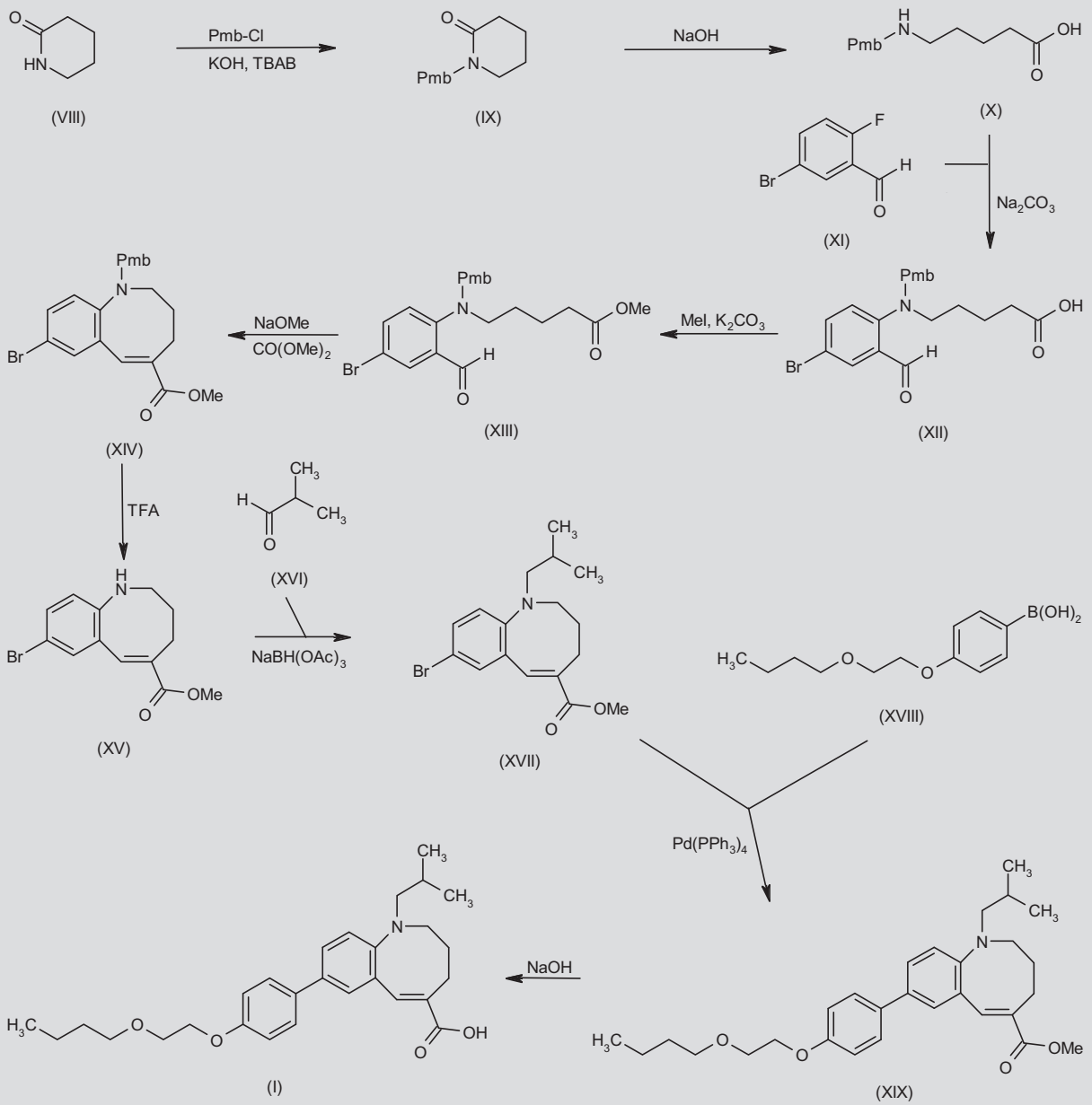
*Synthesis prepared by R. Pandian, C. Estivill, N. Díaz. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

Scheme 1. Synthesis of Cenicriviroc Mesilate



Scheme 2. Synthesis of Intermediate (I)

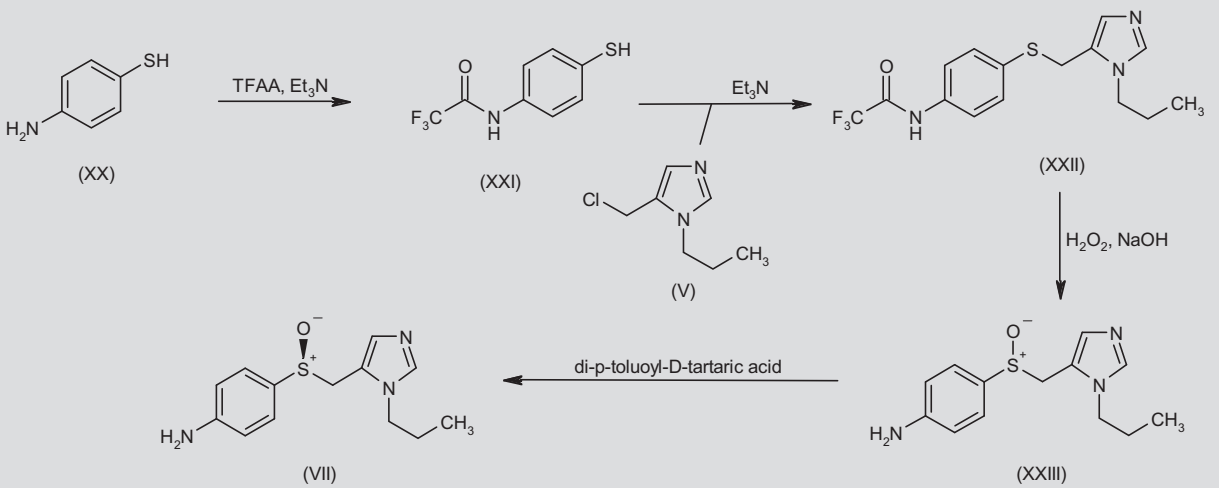


5-(chloromethyl)-1-propylimidazole (V) in the presence of NaOH in MeOH yields thioether (VI). After oxidation of (VI) with mCPBA in CH_2Cl_2, the resulting racemic sulfoxide is resolved employing chiral HPLC to furnish the target (*S*)-enantiomer, which is then treated with MsOH in EtOAc to afford cenicriviroc mesilate (2). In another strategy, acyl chloride (II) couples with the substituted aniline (VII) in the presence of DIEA in THF (1) or Et_3N in THF (3) to yield cenicriviroc, which is then reacted with MsOH in methyl isobutyl ketone, producing the target cenicriviroc mesilate (1, 3). Scheme 1.

Synthesis of intermediate (I):

N-Protection of 2-piperidone (VIII) with PMB-Cl using KOH and TBAB in toluene gives *N*-PMB-2-piperidone (IX), which is then hydrolyzed with NaOH to afford 5-(4-methoxybenzylamino)pentanoic acid (X).

Scheme 3. Synthesis of Intermediate (VII)



Condensation of amine (X) with 5-bromo-2-fluorobenzaldehyde (XI) by means of Na_2CO_3 in DMSO/H_2O then provides the tertiary amine (XII). Methylation of carboxylic acid (XII) with MeI in the presence of K_2CO_3 leads to the corresponding methyl ester (XIII), which then undergoes intramolecular cyclization by means of NaOMe and $CO(OMe)_2$ to yield the *N*-PMB-1-benzazocine derivative (XIV). Debenzylation of compound (XIV) by means of TFA in toluene affords *N*-unsubstituted benzazocine (XV), which is then reductocondensed with isobutyraldehyde (XVI) by means of $NaBH(OAc)_3$ in CH_2Cl_2, affording the 1-isobutyl derivative (XVII). Suzuki coupling of the 8-bromo-1-benzazocine derivative (XVII) with 4-(2-butoxyethoxy) phenylboronic acid (XVIII) by means of $Pd(PPh_3)_4$ provides adduct (XIX). Finally, hydrolysis of methyl ester (XIX) with NaOH in THF/MeOH gives the target carboxylic acid (I) (3). Scheme 2.

Synthesis of intermediate (VII):

Reaction of 4-sulfanylaniline (XX) with TFAA in the presence of Et_3N in THF gives trifluoroacetamide (XXI), which then condenses with 5-(chloromethyl)-1-propylimidazole (V) using TEA in MeOH/H_2O to yield thioether (XXII). Oxidation of sulfanyl derivative (XXII) by means of H_2O_2 in AcOH, followed by hydrolysis with NaOH affords the racemic sulfinyl derivative (XXIII), which is then submitted to optical resolution with di-*p*-toluoyl-D-tartaric acid to provide the desired (*S*)-enantiomer (VII) (1). Scheme 3.

BACKGROUND

HIV-1 remains a serious health problem around the world, and efforts to develop anti-HIV-1 agents are being made by many pharmaceutical companies. Combination chemotherapy using three types of anti-HIV-1 agents, known as HAART (highly active antiretroviral therapy), has led to the achievement of long-term, virtually complete suppression of viral replication in HIV-1-infected individuals and reduction of mortality (4-7). However, difficult dosing regimens, the emergence of drug-resistant HIV-1 and long-term adverse effects have focused the attention in a different direction (3). Over the last few years, HIV attachment and entry inhibitors have received an increased amount of attention as a promising new class of antiretrovirals (8).

Since the chemokine CCR5 receptor was found to be a coreceptor for entry of macrophage-tropic (CCR5-using, R5) HIV-1 into host cells in 1996 (9, 10), many pharmaceutical companies started searching for CCR5 receptor antagonists for the treatment and prevention of HIV-1 (11). Some data support the idea that this new generation of HIV entry inhibitors are also allosteric modulators of the CCR5 receptor (12). However, although there might be beneficial aspects of the blockade of CCR5 function by CCR5 entry inhibitor modulators, such as the blockade of the inflammatory effects of CCR5 activation, it remains unclear whether sparing natural chemokine function for CCR5 systems would be beneficial or detrimental therapeutically.

In 1999, a small-molecule CCR5 receptor antagonist, TAK-779, was reported to be a remarkably potent and selective inhibitor of HIV-1 replication (13). However, this compound could not be developed further because of its poor oral bioavailability (7, 14). Later on, further investigation led to cenicriviroc mesilate (TBR-652, formerly TAK-652), an orally bioavailable TAK-779 derivative with even more potent anti-HIV-1 activity (7, 8, 14, 15).

Cenicriviroc mesilate is a novel, potent, orally active inhibitor of ligand binding to the chemokine CCR5 receptor that also has the unique property of being a CCR2 antagonist (7, 16). In fact, the

CCR2/C-C motif chemokine 2 (monocyte chemotactic protein 1, MCP-1) pathway appears to be active in a large number of diseases and inflammatory disorders, and blocking CCR2 may be an additional advantage for immunocompromised HIV-1-infected patients (17). It has been suggested that cenicriviroc mesilate interacts with the chemokine receptor but not with its ligands (7).

Cenicriviroc mesilate has a promising pharmacokinetic profile, including a long half-life in plasma, suggesting that once-daily administration may be sufficient (7, 18). Cenicriviroc mesilate is generally well tolerated and no adverse effects have been observed (7, 19). On the other hand, an R5 HIV-1 virus highly resistant to this novel CCR5 receptor antagonist has been isolated using a long-term culture of infected peripheral blood mononuclear cells (PBMCs) (20). There may be no exceptions where drug-resistant HIV-1 strains will emerge under the selective pressure of any single antiretroviral agent; however, in a clinical setting, cenicriviroc mesilate must be used in combination with other antiretrovirals (21), which may alter this pattern for the appearance of resistant virus.

PRECLINICAL PHARMACOLOGY

Cenicriviroc mesilate was highly effective against HIV-1 in vitro (3, 7, 14, 22). In an initial study, cenicriviroc mesilate exhibited highly potent CCR5 receptor antagonist activity and strongly inhibited the replication of six strains of R5 HIV-1 using PBMCs (15). Similarly, cenicriviroc mesilate inhibited the replication of six R5 HIV-1 clinical isolates, including reverse transcriptase- and protease inhibitor-resistant mutants, but not X4 HIV-1 replication (3, 7, 14). In CCR5-expressing cells, cenicriviroc mesilate inhibited the binding of RANTES to CCR5 in a concentration-dependent manner. It also blocked the binding of MIP-1α and MIP-1β to CCR5. It slightly suppressed ligand binding to CCR3- and CCR4-expressing cells, although it did not affect the binding of RANTES and MIP-3β to CCR1- and CCR7-expressing cells. Interestingly, cenicriviroc mesilate inhibited the binding of MCP-1 to CCR2. In the same study, all recombinant HIV-1 strains with seven different subtype envelope proteins were equally susceptible to cenicriviroc mesilate. The antiviral activity of cenicriviroc mesilate decreased fivefold in the presence of high concentrations of human serum. No toxicity was seen in vitro at high concentrations, and it is therefore thought to possess low cytotoxicity.

Antiviral interactions between cenicriviroc mesilate and zidovudine, lamivudine, indinavir, efavirenz and enfuvirtide were evaluated in vitro, with promising results showing synergy or additive activity for cenicriviroc mesilate with all other agents at high drug concentrations (8). Moreover, cenicriviroc mesilate also displayed either additive or synergistic activity when used in combination with lopinavir, darunavir, atazanavir, tenofovir, etravirine and raltegravir (22). No antagonism and no cytotoxicity were observed in any two-drug combination at any concentration tested.

Another study showed, both in vitro and in a well-established in vivo model of inflammation, that cenicriviroc mesilate potently inhibited the CCR2 receptor, a chemokine receptor associated with inflammation, and in consequence, cenicriviroc mesilate could be considered a dual CCR5/CCR2 receptor antagonist, which may have significant benefit in HIV-1-infected patients (16).

PHARMACOKINETICS AND METABOLISM

Single oral doses of cenicriviroc mesilate were administered to rats, dogs and monkeys to evaluate the absorption, distribution, metabolism and excretion profile in these species. Cenicriviroc mesilate was well absorbed in all species, although its oral bioavailability was affected by feeding. In fact, feeding decreased the bioavailability in rats and dogs but not in monkeys (3, 23).

A single-dose phase I trial conducted in fasted healthy male volunteers revealed good oral absorption and a rather long half-life in plasma. For all doses, cenicriviroc mesilate was detectable in plasma at 30 minutes and 24 hours post-dose (7).

A similar multiple-dose study was also conducted in healthy volunteers. Cenicriviroc mesilate was administered in two different tablet formulations once daily after a high-fat meal. Cenicriviroc mesilate was well tolerated in all groups and plasma concentrations increased nearly or more than proportionally to dose, with a half-life in plasma ranging from 40 to 45 hours (24). Similar results were obtained after oral administration of a wide range of doses of cenicriviroc mesilate to healthy fasted volunteers, where a half-life in plasma of approximately 32-39 hours was observed (23).

Similarly, a study of two formulations of oral cenicriviroc mesilate in fasted healthy volunteers (single-ascending-dose study) demonstrated that absorption was similar across most groups, while elimination showed linear kinetics (18, 25). Comparable results were found in a multiple-ascending-dose study (18). Cenicriviroc mesilate was safe and well tolerated in both studies.

In parallel, in an open-label, two-part, crossover study to investigate the effect of food on the pharmacokinetics and safety of cenicriviroc mesilate, healthy overnight-fasted volunteers received a single dose of cenicriviroc mesilate either after a high- or a low-fat breakfast. The results showed that a high-fat meal significantly increased the bioavailability and reduced intersubject plasma concentration variability of cenicriviroc mesilate. However, cenicriviroc mesilate plasma concentrations were well above target with or without food (26).

A dose-escalating study where cenicriviroc mesilate was administered as monotherapy given orally for 10 days was conducted in HIV-1-infected, antiretroviral treatment-experienced, CCR5 antagonist-naive patients. Exposure levels of cenicriviroc mesilate increased in a more than dose-proportional manner, while the half-life in plasma increased with increasing doses (27).

Interestingly, among all the studies, cenicriviroc mesilate was well absorbed following either single or repeated dosing in both healthy and HIV-1-infected volunteers and the pharmacokinetic profile of cenicriviroc mesilate in healthy subjects was similar to that observed in HIV-1-infected patients under fed and fasted conditions (28).

SAFETY

Cenicriviroc mesilate was generally safe and well tolerated at the doses studied in both healthy (7, 18, 22, 25) and HIV-1-infected subjects (19, 27, 29, 30). No dose-limiting toxicities have been identified thus far (23, 27). The most common adverse effects found in the subjects were headache and gastrointestinal disorders, and most were mild or moderate in intensity (7, 18, 19, 25). No life-threatening adverse effects were encountered and no adverse effects were judged to be definitely related to the study drug (19).

CLINICAL STUDIES

A double-blind, randomized, placebo-controlled, dose-escalating study to assess the antiviral activity, safety, tolerability and pharmacokinetics of cenicriviroc mesilate was conducted in early 2010 in the U.S. and Argentina. Cenicriviroc mesilate was given orally once daily for 10 days to HIV-1-infected, antiretroviral treatment-experienced, CCR5 antagonist-naive, CCR5-positive patients (19, 27, 29, 30). Virological responses showed a clear dose–response, with all patients receiving 75 mg of cenicriviroc mesilate having a viral load reduction of at least 1 log (30). In fact, significant viral load suppression persisted during the 30-day observation period (27). Cenicriviroc mesilate was confirmed as a potent CCR2 receptor antagonist by significant changes in MCP-1 levels compared to baseline (28). Cenicriviroc mesilate showed potent antiviral activity after 10 days of once-daily monotherapy. In addition, the antiviral effect persisted well into the post-treatment period, with HIV-1 RNA levels still significantly lower for all cenicriviroc mesilate dose groups 5 days after treatment was discontinued and significantly lower than baseline in the 150-mg dose group 2 weeks after treatment discontinuation (19).

A phase IIb study that will enroll treatment-naive patients is planned to test and clarify the best dose for a future phase III study (19).

DRUG INTERACTIONS

Drug–drug interaction studies are under way to enable the construction of a combination regimen with an appropriate cenicriviroc mesilate dose (19). However, it is anticipated that cenicriviroc mesilate will prove to be a good candidate for coformulation with other once-daily antiretroviral agents, given the once-daily, low-dose profile and good tolerability exhibited by the drug so far.

SOURCES

Originated by Takeda Pharmaceutical Co., Ltd. (JP); licensed exclusively worldwide to Tobira Therapeutics, Inc. (US).

DISCLOSURES

The author states no conflicts of interest.

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