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Vicriviroc

Rec INN; USAN

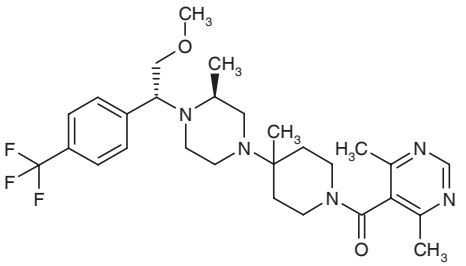
Anti-HIV Agent
Viral Entry Inhibitor
Chemokine CCR5 Antagonist

SCH-D
SCH-417690

1-(4,6-Dimethylpyrimidin-5-yl)-1-[4-[4-[2-methoxy-1(*R*)-[4-(trifluoromethyl)phenyl]ethyl]-3(*S*)-methylpiperazin-1-yl]-4-methylpiperidin-1-yl]methanone

5-[4-[4-[2-Methoxy-1(*R*)-[4-(trifluoromethyl)phenyl]ethyl]-3(*S*)-methylpiperazin-1-yl]-4-methylpiperidin-1-ylcarbonyl]-4,6-dimethylpyrimidine

InChI=1/C28H38F3N5O2/c1-19-16-35(14-15-36(19)24-17-38-5)22-6-8-23(9-7-22)28(29,30)31)27(4)10-12-34(13-11-27)26(37)25-20(2)32-18-33-21(25)3/h6-9,18-19,24H,10-17H2,1-5H3/t19-,24-/m0/s1



$C_{28}H_{38}F_3N_5O_2$
Mol wt: 533.629

CAS: 306296-47-9

CAS: 599179-03-0 (maleate salt [1:1])

EN: 352312

Abstract

Vicriviroc is a viral entry inhibitor under development for the treatment of HIV-1 infection in combination with other antiretrovirals. It is a small-molecule antagonist of the chemokine receptor CCR5, which is expressed on the surface of macrophages and leukocytes and is required for the efficient entry of R5-tropic HIV into target cells. Vicriviroc has potent activity against a wide range of primary HIV-1 isolates and an excellent pharmacokinetic profile. In a phase II clinical trial, vicriviroc was associated with treatment failures in combination with the reverse transcriptase inhibitors lamivudine/zidovudine (Combivir®), whereas in another phase II trial, vicriviroc (10 mg once daily and above) was effective in reducing HIV viral load and increasing $CD4^+$ counts in combination with optimized background therapies containing ritonavir (which boosts the pharmacokinetics of vicriviroc) and a protease inhibitor.

Synthesis

Vicriviroc can be synthesized as follows:

The condensation of piperazine (I) with 1-Boc-4-piperidone (II) in the presence of diethylaluminum cyanide and titanium isopropoxide in refluxing dichloromethane gives the aminonitrile adduct (III), which undergoes cyanide group displacement with methylmagnesium bromide to afford the methylated compound (IV). Then, acidic *N*-Boc group cleavage in (IV), followed by acylation of the deprotected piperidine (V) with 4,6-dimethylpyrimidine-5-carbonyl chloride (VI) in the presence of aqueous NaOH in CH_2Cl_2 provides the target vicriviroc (1-4). Alternatively, 4,6-dimethylpyrimidine-5-carboxylic acid (VII) is coupled with 4-piperidone (VIII) (or its hydrate form) via activation with either oxalyl chloride (5) or with mesyl chloride and TMEDA (6) to produce the piperidone amide (IX). This is then condensed with piperazine (I) in the presence of sodium cyanide or acetone cyanohydrin to generate the aminonitrile adduct (X), which is finally converted to the title compound by cyanide displacement with methylmagnesium chloride and trimethylaluminum (6). Scheme 1.

The intermediate 1-[2-methoxy-1(*R*)-(4-trifluoromethylphenyl)ethyl]-2(*S*)-methylpiperazine (I) can be prepared by several related methods. Reaction of 4-(trifluoromethyl)styrene (XI) with *m*-chloroperbenzoic acid in dichloromethane affords the epoxide (XII), which is treated with methanolic NaOMe to yield 2-methoxy-1-(4-trifluoromethylphenyl)ethanol (XIII). After conversion of the benzylic alcohol (XIII) to the racemic mesylate (XIV), condensation with 1-Boc-3(*S*)-methylpiperazine (XV) gives a diastereomeric mixture of alkylated piperazines, from which the target (*R,S*)-isomer (XVI) is isolated utilizing

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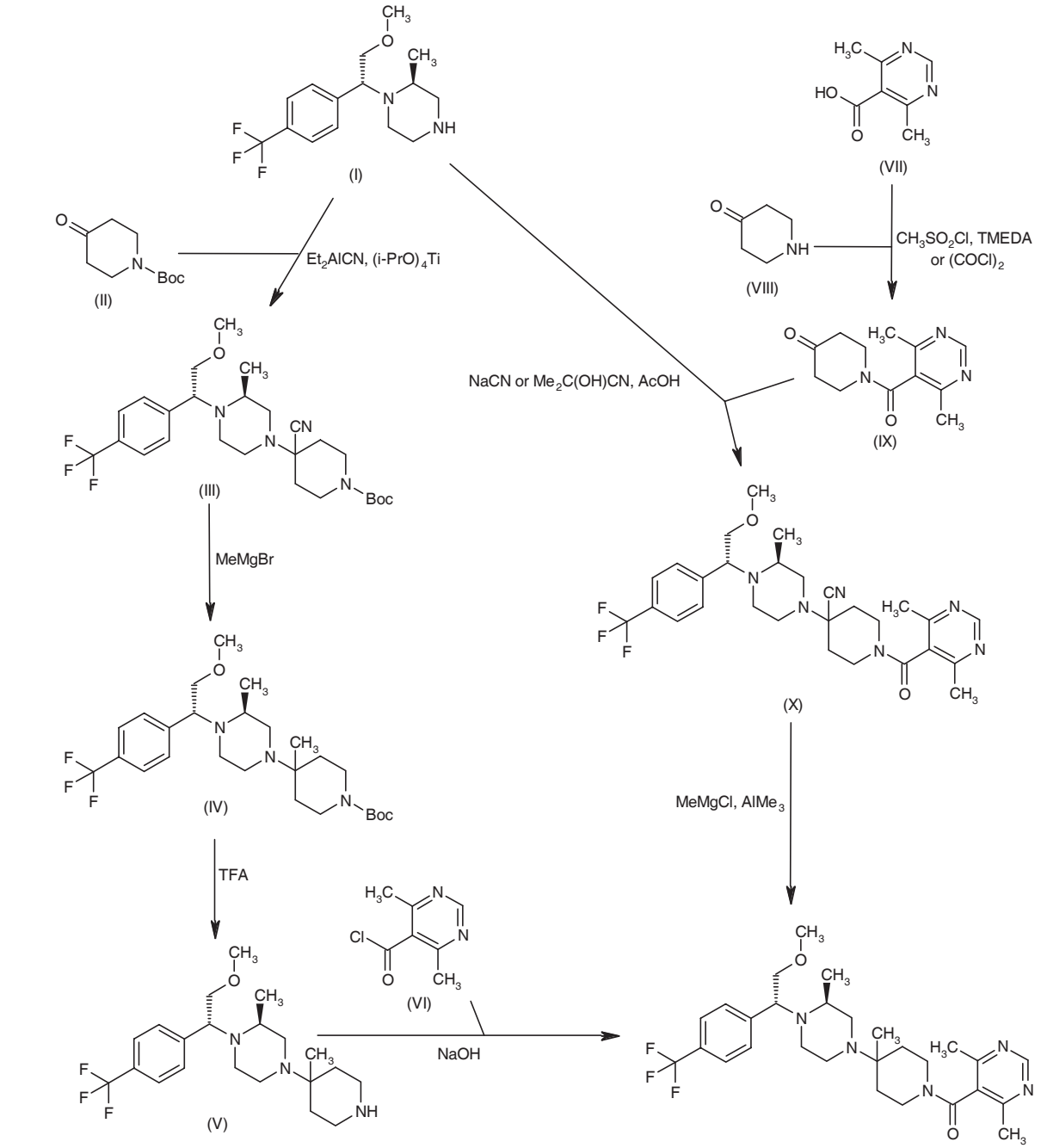
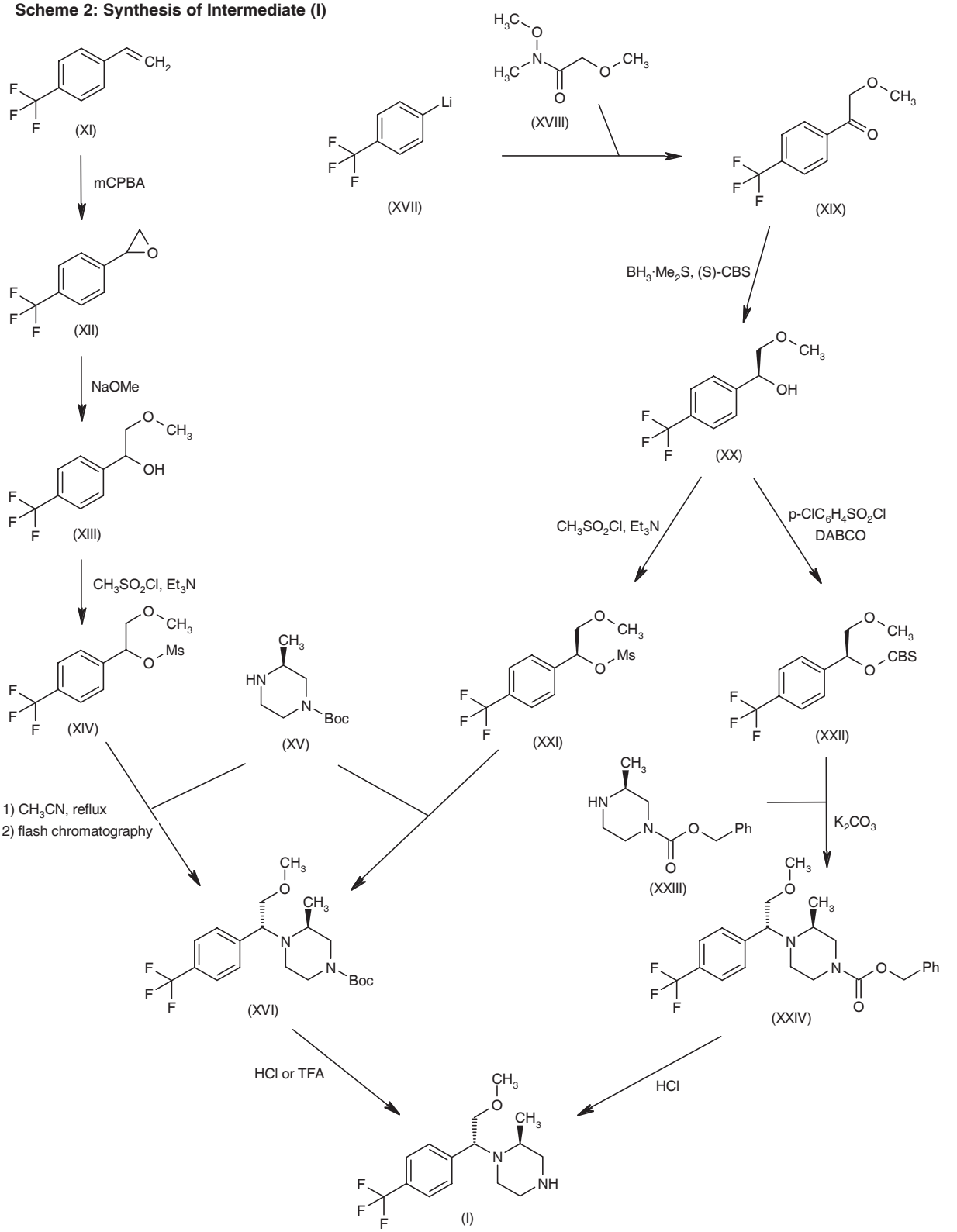
Scheme 1: Synthesis of Vicriviroc



flash chromatography. Then, acidic deprotection of the *N*-Boc piperazine (XVI) furnishes the target intermediate (I) (1-3). Alternatively, addition of 4-trifluoromethylphenyllithium (XVII) to the Weinreb amide of methoxyacetic acid (XVIII) gives the 2-methoxyacetophenone (XIX), which is enantioselectively reduced to the (*S*)-alcohol (XX) utilizing borane-dimethylsulfide complex in the presence of (*S*)-CBS-oxazaborolidine. Conversion of (XX) to the optically active mesylate (XXI), followed by mesylate displacement with piperazine (XV), then furnishes the Boc-protected precursor (XVI) (4). Similarly, treatment of the chiral alcohol (XX) with 4-chlorobenzenesulfonyl chloride in the presence of DABCO gives the corresponding sulfonate (XXII), which is condensed with 1-(benzyloxycarbonyl)-3(*S*)-methylpiperazine (XXIII) by means of K_2CO_3 in toluene/acetonitrile to yield adduct (XXIV). Deprotection of (XXIV) in hot aqueous HCl then provides the desired intermediate (I) (6). Scheme 2.

Scheme 2: Synthesis of Intermediate (I)



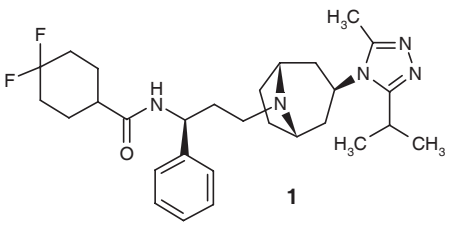
Background

Highly active antiretroviral therapy (HAART) is a powerful anti-HIV therapy based on combinations of at least 3 antiretroviral medications inhibiting reverse transcriptase and protease. Its availability in developed countries has altered the natural history of HIV infection, reducing the morbidity and mortality due to HIV. This success has meant a shift in the emphasis in HIV management; now the focus is less on the reduction of mortality and more on managing HIV as if it were a chronic disease. Issues of patient compliance, drug interactions, toxicity, adverse events, viral resistance and viral reservoirs are of increasing importance, and new antiretroviral medications are being sought with the aim of tackling these components of the disease (7-9).

HIV replication initiates with viral entry into the target T-cell, followed by replication of the viral genome, expression of viral proteins, and then assembly and release of the viral particles. The reverse transcriptase inhibitors target the replication stage, and the protease inhibitors target assembly and release. The approval of enfuvirtide in 2003 demonstrated that HIV entry is also a viable target for therapeutic intervention, and several viral entry inhibitors are currently in clinical development (Table I). Viral entry initiates with the virus attaching to the surface

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

Drug	Source	Phase
1. Maraviroc	Pfizer	Rec approval
2. SP-01A** (Anticort)	Samaritan Pharmaceuticals/Pharmaplaz	III
3. Ibalizumab (TNX-355)**	Tanox	II
4. INCB-9471*	Incyte	II
5. Sifuvirtide	FusoGen Pharmaceuticals	II
6. Vicriviroc	Schering-Plough	II
7. BMS-378806	Bristol-Myers Squibb	I
8. HGS-004**	Human Genome Sciences	I
9. INCB-15050*	Incyte	I
10. KD-247**	Chemo-Sero Ther. Res. Inst./Kumamoto University	I
11. PF-232798*	Pfizer	I
12. PRO-140**	Progenics	I
13. RPI-MN*	Nutra Pharma/ReceptoPharm	I
14. TAK-220	Takeda	I
15. Nifeviroc*	Shanghai Target Drug/Avexa	IND filed



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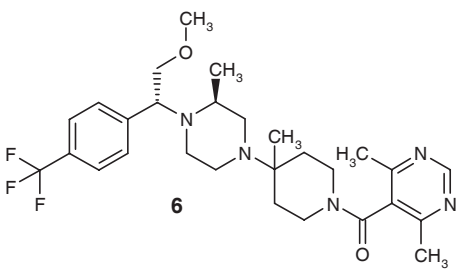

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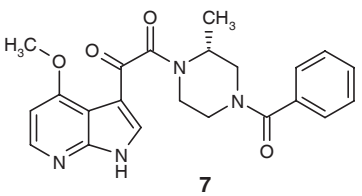

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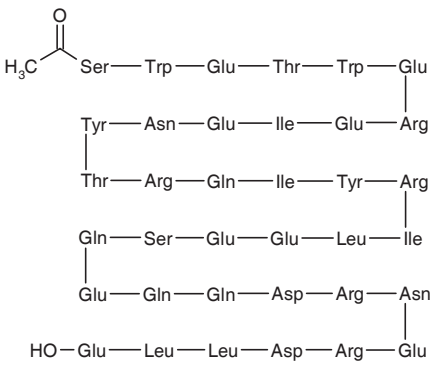

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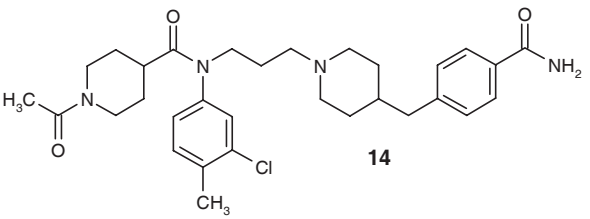

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*Structure not available. **No structure.

of T-cells, followed by interaction between the viral gp120 envelope protein and the T-cell CD4 receptor. This interaction promotes conformational changes in the attachment complex that leads to host cell co-receptors CXCR4 or CCR5 being exposed to the viral gp120. Interactions between the highly variable loops V2 and V3 on the viral gp120 and the co-receptor lead to further conformational changes and the viral and host cell membranes fuse (Figs. 1 and 2). The co-receptor CCR5 mediates the entry of R5-tropic strains of HIV, which are generally responsi-

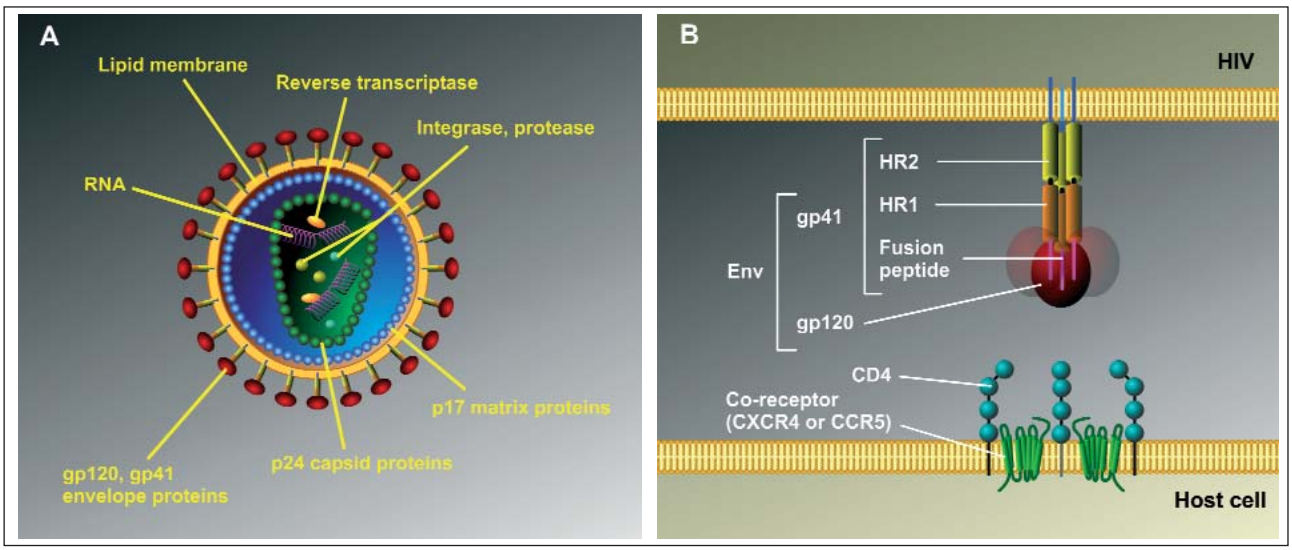

Fig. 1. **A**: The HIV nucleocapsid contains two identical copies of a positive-sense single-stranded RNA and two copies of the reverse transcriptase, together with other viral proteins. The capsid is in turn enclosed in a layer of matrix protein which is associated with a lipid bilayer or envelope containing the proteins necessary for host cell binding. **B**: The envelope complex consists of heterotrimeric spikes formed by gp120 and gp41 glycoproteins, the latter consisting of HR1, HR2 and fusion peptide domains. Critical host proteins required for viral fusion are CD4 and a co-receptor (*i.e.*, CCR5, CXCR4).

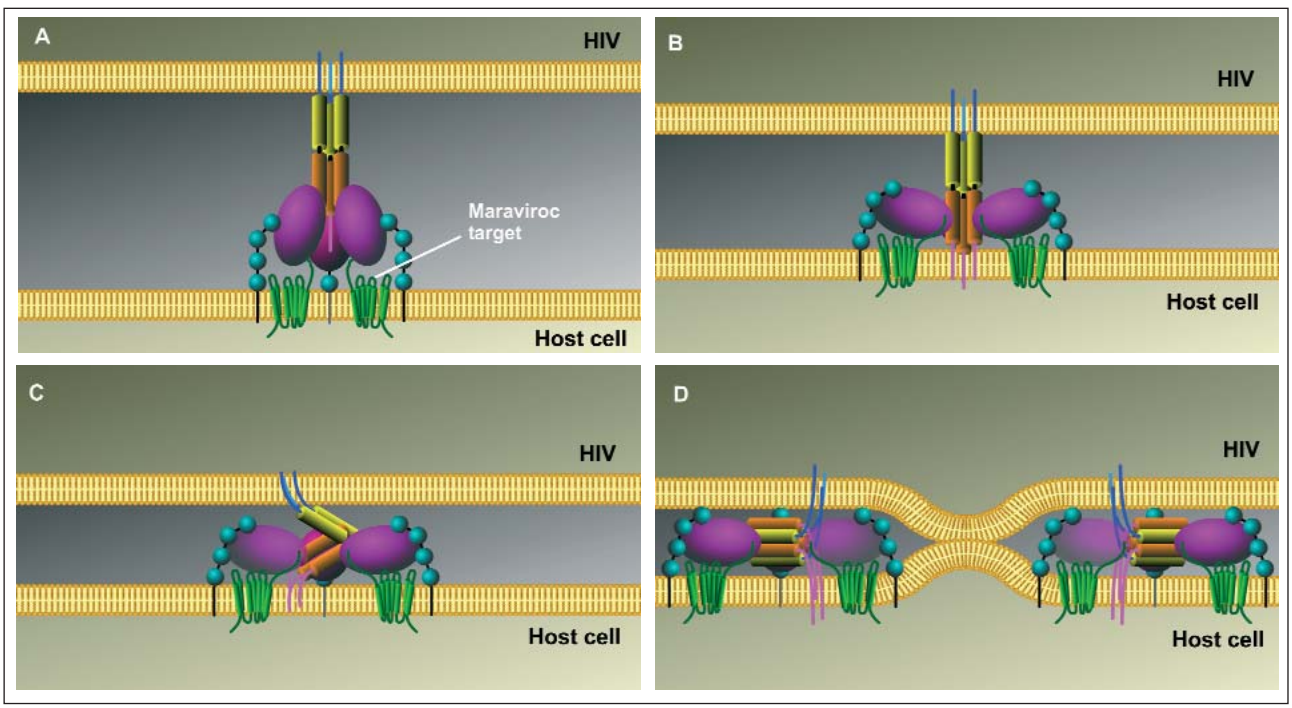

Fig. 2. **A**: Binding of viral gp120 to CD4 induces the first conformational change in gp120 that unmasks the co-receptor binding site. A CCR5 antagonist such as maraviroc binds to CCR5 such that HIV cannot successfully bind with the co-receptor, thus preventing viral entry and infection. **B**: Binding of gp120 to the co-receptor induces the second conformational change in gp120, in response to which the fusion peptide is inserted into the host cell membrane. **C**: HR1 and HR2 form a six-helix bundle. **D**: This juxtaposes the viral and cellular membranes, resulting in pore formation and membrane fusion.

ble for establishing infection, as they are more efficiently transmitted than X4-tropic strains. The CXCR4 receptor is the route of entry for the X4-tropic strains, which appear in the late stages of the disease and are associated with a rapid progression to AIDS. R5/X4 dual-tropic strains are also present in the late stages of the disease; these strains are able to use both co-receptors, although predominantly CXCR4 (10-12).

CCR5 is also an attractive target because it is a G-protein-coupled receptor, classically a good target for drug development, it is dispensable (individuals homozygous for a CCR5Δ32 mutation produce an inactive co-receptor and are apparently healthy), and gene polymorphisms encoding CCR5 with reduced activity are linked to increased resistance to HIV infection. Several agents that target CCR5 are in clinical development for the treatment of patients with R5-tropic HIV-1 infections, including maraviroc, INCB-9471, INCB-15050, PF-232798 and TAK-220 (see Table I) (10, 12, 13). Vicriviroc (SCH-417690) is an orally available, small-molecule CCR5 co-receptor antagonist in development for the treatment of HIV-R5-infected patients in combination with current antiretroviral agents (4, 10-13).

Preclinical Pharmacology

Vicriviroc was obtained as part of a backup program to an earlier CCR5 inhibitor, SCH-C (SCH-351125). Lead optimization of the benzylic substituent resulted in a compound with high potency against a range of HIV-1 isolates (EC_{50}/IC_{50} < 10 nM) in peripheral blood mononuclear cells (PBMCs) and high selectivity for the CCR5 receptor (K_i = 2.5 nM *vs.* > 10,000 nM for muscarinic M_1 and M_2 receptors). The compound inhibited HIV entry in U-80 cells with an IC_{50} of 0.46 nM. It was also highly active against resistant HIV, including enfuvirtide-, protease inhibitor-, reverse transcriptase inhibitor- and multidrug-resistant strains, with EC_{50} values of 8.7-32.9 nM and fold change in EC_{50} values of < 2-fold. As expected, vicriviroc was not active against X4- or dual R5/X4-tropic HIV-1 strains. The dissociation constant (K_d) for vicriviroc for CCR5 binding is 0.4 nM (0.18 nM for maraviroc) and the dissociation half-life is 12 h (7.5 h for maraviroc). In functional assays, vicriviroc inhibited calcium flux, GTPγS binding and chemotaxis induced by RANTES, MIP-1α and MIP-1β, confirming CCR5-antagonist activity. No toxicity was observed in cell cultures at concentrations up to 10 μM (4, 14-17).

Vicriviroc showed additive or synergistic interactions in combination with approved antiviral agents from other classes. The agents tested were zidovudine, lamivudine (nucleoside reverse transcriptase inhibitors), efavirenz (non-nucleoside reverse transcriptase inhibitor), indinavir (protease inhibitor) and enfuvirtide (fusion inhibitor). In the presence of vicriviroc and each of the approved antiretroviral therapeutics at the EC_{90} or above (concentrations considered likely to be achieved clinically), the combination indices (CI) ranged from 0.37 to 0.84, indicating synergy (15, 17).

Potential interactions between vicriviroc, maraviroc and the CCR5 monoclonal antibody PRO-140 were investigated in two cell-based assays of HIV-1 viral entry. In an HIV-1-mediated membrane fusion assay, vicriviroc was synergistic with PRO-140 (CI for 50% inhibition [CI_{50}] = 0.51; CI_{90} = 0.36). In an HIV-1 pseudovirus assay measuring combined entry and reverse transcriptase activity, vicriviroc was again synergistic with PRO-140 (CI_{50} = 0.47; CI_{90} = 0.18). When tested in competition binding assays, vicriviroc acted as a partial antagonist of PRO-140 binding, providing a mechanistic explanation for the synergy (16).

The selection of vicriviroc-resistant mutants *in vitro* required prolonged periods of serial passage of virus in human PBMCs in the presence of increasing concentrations of the drug. In one study, 15-fold resistance was obtained after > 30 passages of HIV-1_{JR-FL} in the presence of drug. Vicriviroc-resistant viral strains generally remained R5-tropic; all were cross-resistant to other anti-CCR5 compounds but remained sensitive to inhibition by other anti-HIV agents. Sequence analysis revealed multiple changes in the gp120- and gp41-encoding regions of the *env* gene (18-21).

Pharmacokinetics and Metabolism

In rats (10 mg/kg) and monkeys (2 mg/kg), when administered by i.v. injection or by oral gavage, vicriviroc showed good absorption (100% and 95% for rats and monkeys, respectively) and oral bioavailability (100% and 89%, respectively). The agent displayed good CNS penetration (brain/plasma ratio = 0.86). The major route of metabolism in rats is *O*-demethylation of the methoxy side-chain followed by glucuronidation in the liver. In monkeys receiving 2 mg/kg vicriviroc, the C_{max} was 1.3 μM, 200-fold higher than the mean antiviral EC_{90} *in vitro*. The half-life was 3.4 h in monkeys and 7.9 h in rats (4, 15).

$CCR5^+CD4^+$ T-lymphocytes predominate in the gut-associated lymphoid tissue (GALT), and their numbers are rapidly depleted at this site during the early stages of HIV-1 infection. The distribution of orally administered vicriviroc was determined in rats and the rank order of cumulative vicriviroc exposure was spleen > GALT > lymph node > lungs > blood. A single 5 mg/kg dose gave drug concentrations in the GALT that were 10-1,000-fold higher than the target IC_{90} (6 nM) over 48 h (22).

To determine the extent of vicriviroc distribution into maternal milk, and hence from the milk to the pups, 18 post-partum rats were dosed with 5 mg/kg vicriviroc maleate as an oral solution. Pharmacokinetic analysis showed a milk:plasma ratio in dams of about 2-4. A maximum of 0.5% of the dose administered to dams was detected in the pups over 0-48 h (23).

Vicriviroc metabolism studies performed *in vitro* showed *O*-demethylation, *N,N*-dealkylation, *N*-dealkylation and carboxylic acid formation, primarily mediated by cytochrome P-450 CYP3A4. Vicriviroc did not inhibit the activities of the major CYP enzymes *in vitro* at concentra-

tions up to 26.7 μg/ml, 100 times the expected clinically relevant dose, indicating that it is unlikely to affect the metabolism of other co-administered drugs. In clinical studies, the combination of vicriviroc (10 mg p.o. once daily) with ritonavir (a potent CYP3A4 inhibitor; 100 mg once daily or above) resulted in increased C_{max} and AUC values for vicriviroc compared to vicriviroc alone. This is consistent with the observed *in vitro* CYP3A4-mediated metabolism of vicriviroc (24).

The metabolism and excretion of vicriviroc were also compared in humans, monkeys and rats. Single oral doses of vicriviroc were administered as follows: 50 mg in humans, 5 mg/kg in monkeys and 6 mg/kg in rats. The radioactivity was distributed nearly equally between feces and urine in humans, whereas there was a greater proportion in the feces of rats and monkeys. Analysis of the excreted material showed that metabolism was qualitatively similar in all species, and the major excreted substance was unchanged drug. Vicriviroc was metabolized by *O*-demethylation, *N*-dealkylation, oxidation and glucuronidation (25).

In a randomized, open-label, single-dose, crossover study, 20 healthy adults received 50 mg oral vicriviroc under fasting conditions and with a standardized high-fat meal. Administration of vicriviroc with a high-fat meal decreased the rate of absorption of the drug (C_{max} approximately 60% of that seen in fasted subjects; t_{max} delayed from 1 to 3 h), but did not affect the overall exposure (AUCs were similar at 1970 and 2090 ng.h/ml for the fasted and fed states, respectively). The mean terminal $t_{1/2}$ was similar in the fasted and fed states (19.1-43.3 and 17.4-41.7 h, respectively) (26).

In two phase I multiple-dose assessments of vicriviroc, 36 uninfected and 47 HIV-infected subjects were randomized (4:1) to vicriviroc (10, 25 or 50 mg) or matching placebo twice daily for 14 days. Vicriviroc exposure increased in a dose-linear manner, with no significant differences in the pharmacokinetic parameters between the uninfected and infected subjects; the mean $t_{1/2}$ was 24 h or greater. Vicriviroc was well tolerated in both populations and there were no dose-related adverse events (27).

Safety

The forerunner to vicriviroc, SCH-C, also a piperazine-based CCR5 antagonist, was associated with Q-T prolongation in healthy human volunteers. In the voltage clamp assay, vicriviroc attenuated the human ether a-go-go related gene transcript ion channel (hERG) with an IC_{50} of 5.8 μM compared to 1.1 μM for SCH-C. When tested in cynomolgus monkeys, no Q-T prolongation was observed at doses of vicriviroc of up to 40 mg/kg (4, 15). In chronic dosing studies in rats, no adverse effects were observed and liver enzymes were neither inhibited nor induced. There were no acute CNS or gastrointestinal effects of vicriviroc in rats (10 mg/kg orally) (4).

The cardiac safety profile of vicriviroc was examined using pooled data from several phase I studies. In all, 63 subjects (healthy and HIV-infected) received a single dose of vicriviroc (10-150 mg) and 85 subjects received multiple doses for 14 days (10-50 mg twice daily). The mean changes in Q-T_{cF} interval ranged from –4.5 to +5.4 ms on active treatment, and no subject had a Q-T_{cF} interval of 500 ms or greater, indicating that vicriviroc does not prolong cardiac repolarization (28). The results from this and several of the following studies are summarized in Table II.

Clinical Studies

Using a mathematical pharmacokinetic/pharmacodynamic disease model, a once-daily oral dose of 30 mg vicriviroc in combination with lamivudine/zidovudine (Combivir®) + ritonavir was predicted to provide antiviral activity comparable to the current standard of care. Greater vicriviroc exposure was predicted to provide greater antiviral activity (29).

A 2-week, parallel-group study examined the efficacy of vicriviroc as monotherapy in HIV-infected patients. Forty-eight patients with $CD4^+$ cell counts of > 200/mm^3 were assigned to 3 groups and randomized to receive either vicriviroc (10, 25 or 50 mg) or placebo twice daily for 14 days. The steady-state C_{max} values were 120, 270 and 525 nM, respectively, in the 10-, 25- and 50-mg active treatment groups and C_{min} values remained above the IC_{90} for vicriviroc. The mean change in viral load was –1.08, –1.56 and –1.62 $\log_{10}$ copies/ml, respectively; $CD4^+$ counts also increased. After completion of dosing, the HIV load returned slowly towards baseline. The treatment was well tolerated (30, 31).

To evaluate the effect of long-term therapy with vicriviroc + Combivir®, 92 R5-tropic HIV-positive, treatment-naïve subjects were randomized to vicriviroc (25, 50 or 75 mg) or placebo once daily for 14 days (study protocol P03802). Combivir® was then added to each regimen, and placebo was replaced by open-label efavirenz. The study was terminated after a mean patient follow-up of 32 weeks due to treatment failures; 8% of those receiving efavirenz had virological breakthrough (RNA = 50 copies/ml or more), whereas 57%, 45% and 22% of those on 25, 50 and 75 mg vicriviroc, respectively, had virological breakthrough. Resistance was due to the emergence of treatment-related M184V mutations (32). Analysis of multiple viral parameters at baseline and at breakthrough, including IC_{50} values, fold change to reference virus, percent maximal viral suppression and patterns of mutation in the viral envelope sequences, could not entirely explain late viral breakthrough (32, 33).

A long-term, double-blind phase II study (ACTG5211) is examining the safety and efficacy of vicriviroc in HIV-infected patients with drug resistance. In a preliminary report, 118 patients had been randomized to vicriviroc (5, 10 or 15 mg) or placebo once daily for 14 days in addition to an optimized background therapy (OBT); the lowest dose was discontinued early on. At day 14 and week 24, both doses were associated with a greater decrease in viral load compared to placebo, with no difference between the two vicriviroc treatment groups. Grade 3/4

Table II: Clinical studies of vicriviroc (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions/Objectives	Ref.
HIV infection	Pooled/meta-analysis	Vicriviroc, 10 mg (n=6) Vicriviroc, 25 mg (n=6) Vicriviroc, 50 mg (n=26) Vicriviroc, 100 mg (n=6) Vicriviroc 150 mg (n=13) Vicriviroc, 10 mg b.i.d. (n=40) Vicriviroc, 25 mg b.i.d. (n=22) Vicriviroc, 50 mg b.i.d. (n=20) Placebo (n=50)	190	No vicriviroc-related changes in Q-T_c interval duration were found in HIV-infected and healthy subjects	28
HIV infection	Randomized Double-blind	Vicriviroc, 10 mg p.o. b.i.d. x 14 d (n=12) Vicriviroc, 20 mg p.o. b.i.d. x 14 d (n=12) Vicriviroc, 50 mg p.o. b.i.d. x 14 d (n=12) Placebo (n=12)	48	Vicriviroc was well tolerated and dose-dependently reduced the viral load in patients with chronic HIV infection	30, 31
HIV infection	Randomized Multicenter	Vicriviroc, 25 mg o.d. x 14 d → Id. + Lamivudine + Zidovudine x 46 wks Vicriviroc, 50 mg o.d. x 14 d → Id. + Lamivudine + Zidovudine x 46 wks Vicriviroc, 75 mg o.d. x 14 d → Id. + Lamivudine + Zidovudine x 46 wks Placebo x 14 d → Efavirenz + Lamivudine + Zidovudine x 46 wks	92	Vicriviroc demonstrated excellent antiviral activity and tolerability when administered alone, but was not associated with durable suppression of plasma HIV RNA when given in combination with lamivudine/zidovudine in patients with HIV infection	32
HIV infection	Randomized Double-blind	Vicriviroc, 5 mg/d x 14 d Vicriviroc, 10 mg/d x 14 d Vicriviroc, 15 mg/d x 14 d Placebo	118	Reductions in HIV-1 RNA in infected patients were similar between vicriviroc doses and significantly greater with each vicriviroc dose compared to placebo at day 14 and at week 24	34, 35
HIV infection	Randomized Double-blind Multicenter	Vicriviroc, 20 mg o.d. x 48 wks Vicriviroc, 30 mg o.d. x 48 wks Placebo	120	The safety and efficacy of add-on vicriviroc in HIV-positive patients with suboptimal response to optimized antiretroviral therapy will be determined in a phase II study	36

adverse events were similar across all groups. However, the study was unblinded following the diagnosis of 5 malignancies, including lymphomas, among the vicriviroc-treated patients. The relationship to vicriviroc treatment was uncertain (34, 35).

A 1-year, randomized, placebo-controlled, parallel-group, double-blind phase II study (VICTOR-E1, Vicriviroc In Combination Treatment with Optimized antiretroviral treatment Regimen in Experienced subjects) of vicriviroc (20 or 30 mg once daily) *versus* placebo in combination with an OBT regimen (containing ritonavir and a protease inhibitor) in treatment-experienced patients was initiated in June 2006 and has completed enrollment (36). One phase III trial of vicriviroc added to OBT in treatment-experienced HIV-infected patients (VICTOR-E2) was terminated (37), but another (VICTOR-E4) is expected to commence enrollment soon (38).

Drug Interactions

Vicriviroc showed no significant *in vitro* interactions with the P-glycoprotein multidrug efflux pump. This suggests that co-administration with P-glycoprotein inhibitors is unlikely to cause drug interactions (39).

A series of open-label, randomized, placebo-controlled, crossover studies evaluated drug interactions with approved HIV treatments. In one study, the effect of ritonavir (a CYP3A4 inhibitor) on vicriviroc plasma exposure was studied in 46 healthy adult subjects (n=9/group) who received either vicriviroc (10 mg twice daily) alone or in combination with ritonavir (100 mg once daily, 100 mg twice daily, 200 mg twice daily or 400 mg twice daily) for 14 days. Ritonavir boosted vicriviroc exposure, with C_{max} values increased about 350% and $AUC_{0\text{-}12h}$ increased about 500% compared to vicriviroc alone, regardless of the ritonavir dose (40, 41).

In another study, 24 healthy adult subjects received vicriviroc (10 mg), vicriviroc + ritonavir (100 mg) or vicriviroc + ritonavir/lopinavir (Kaletra®; 400 mg) once daily for 14 days. By day 14, the vicriviroc C_{max} values were increased 2.5-fold and $AUC_{0\text{-}24h}$ was increased 5.4-fold in the vicriviroc + ritonavir group compared to vicriviroc alone. There was no further change with the addition of lopinavir (42, 43).

Another study compared vicriviroc (10 mg twice daily) and vicriviroc + tenofovir (300 mg once daily) for 7 days in 24 healthy adult subjects. On day 7, no significant differences in vicriviroc $AUC_{0\text{-}12h}$ or C_{max} were seen between the treatment groups, indicating no drug interactions for this combination (44, 45).

Combinations of vicriviroc with ritonavir (a CPY3A4 inhibitor) and efavirenz (a CYP3A4 inducer) were tested in 36 healthy adults. Subjects received vicriviroc (10 mg), vicriviroc + ritonavir (100 mg), vicriviroc + efavirenz (600

mg) or vicriviroc + ritonavir + efavirenz once daily for 14 days. As expected from previous studies, ritonavir boosted steady-state vicriviroc exposure (C_{max} values increased 208-371% and AUC increased 422-801% compared to vicriviroc alone), whereas efavirenz reduced vicriviroc exposure (AUC 74-86%, C_{max} 56-75%). In combination, the effect of ritonavir was greater than that of efavirenz and the exposure to vicriviroc was increased *versus* vicriviroc alone (C_{max} increased 147-261% and AUC increased 279-529%) (46, 47).

To test the combination of vicriviroc + Combivir®, 36 healthy adult subjects received vicriviroc (50 mg), Combivir® (1 tablet of lamivudine 150/zidovudine 300 mg) or vicriviroc + Combrivir® twice daily for 7 days. There were no significant drug interactions in this study (48, 49).

Healthy volunteers (n=8/group) were exposed to vicriviroc + ritonavir (100 mg once or twice daily) for 14 days, followed by the addition of one of the following protease inhibitors: atazanavir (300 mg once daily), indinavir (800 mg b.i.d.), fosamprenavir (700 mg b.i.d.), nelfinavir (1250 mg b.i.d.) or saquinavir (1000 mg b.i.d.) for a further 14 days (except for atazanavir, 7 days). There was no effect on vicriviroc plasma concentrations after addition of any of the protease inhibitors (50, 51).

Source

Schering-Plough Corp. (US).

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