Drugs of the Future 2005, 30(5): 469-477

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.05.902712

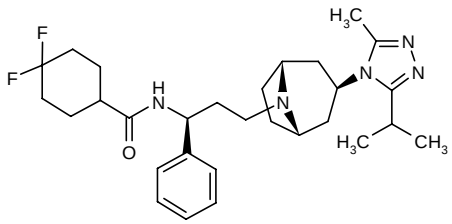
Maraviroc

Prop INN

Anti-HIV Agent
Viral Entry Inhibitor
Chemokine CCR5 Antagonist

UK-427857

4,4-Difluoro-*N*-[3-[(1*R*,3*exo*,5*S*)-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1(*S*)-phenylpropyl]cyclohexanecarboxamide



$C_{29}H_{41}F_2N_5O$

Mol wt: 513.6729

CAS: 376348-65-1

EN: 313738

Abstract

Despite the availability of several approved drugs for the treatment of human immunodeficiency virus (HIV) infection, the limited effectiveness of current antiretroviral regimens, mainly due to the emergence of resistance, makes the development of new agents necessary. Several novel compounds are being added to existing classes, but newer classes of antiretroviral drugs, such as HIV entry inhibitors, are also under development. Maraviroc is a novel small molecule that specifically antagonizes the chemokine CCR5 receptor required for efficient HIV entry. It displays potent and broad-spectrum anti-HIV activity and excellent pharmacokinetic and safety profiles. All these features and the promising results obtained in early clinical trials make this agent a good candidate for inclusion in combination therapies for HIV treatment. Maraviroc is the most clinically advanced CCR5 antagonist and has just entered phase III clinical trials.

Synthesis

Cyclization of 2,5-dimethoxytetrahydrofuran (I) with benzylamine (II) and 2-oxomalonic acid (III) by means of aqueous HCl and NaOAc gives 8-benzyl-8-azabicyclo-[3.2.1]octan-3-one (IV), which is treated with hydroxylamine and pyridine in refluxing ethanol to afford the corresponding oxime (V). Reduction of oxime (V) with Na in refluxing pentanol provides the primary amine (VI), which is acylated with isobutyric acid (VII) and EDC in dichloromethane to yield the isobutyramide (VIII). Cyclization of amide (VIII) with acetic hydrazide (IX) by means of pyridine in chloroform results in the 1,2,4-triazole derivative (X), which is debenzylated by transfer hydrogenolysis with ammonium formate and $Pd(OH)_2$ to afford 3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (XI). The reductocondensation of compound (XI) with 3(*S*)-(*tert*-butoxycarbonylamino)-3-phenylpropionaldehyde (XII) by means of $NaBH(OAc)_3$/AcOH in dichloromethane provides the adduct (XIII), which is *N*-deprotected by means of HCl in refluxing methanol/water to give the primary amine (XIV). Finally, this compound is acylated with 4,4-difluorocyclohexanecarboxylic acid (XV) by means of a carbodiimide polymer (1). Scheme 1.

Intermediate (XII), 3(*S*)-(*tert*-butoxycarbonylamino)-3-phenylpropionaldehyde, can be obtained as follows:

Reaction of 3(*S*)-amino-3-phenylpropionic acid *tert*-butyl ester (XVI) with refluxing methanolic HCl gives the corresponding methyl ester (XVII), which is treated with Boc_2O and NaOH in THF/water to yield the *N*-protected β-amino ester (XVIII). Finally, this compound is reduced by means of diisobutylaluminum hydride in dichloromethane (1). Scheme 2.

Introduction

According to the latest UNAIDS report, there were nearly 40 million people living with HIV/AIDS worldwide in December 2004. This pandemic is continuously expanding, mainly in developing countries, where the socioeconomic impact of the disease is very important (2). In contrast, HIV infection has become a treatable, chronic disease for those infected patients in developed countries who have access to drugs. The introduction of powerful

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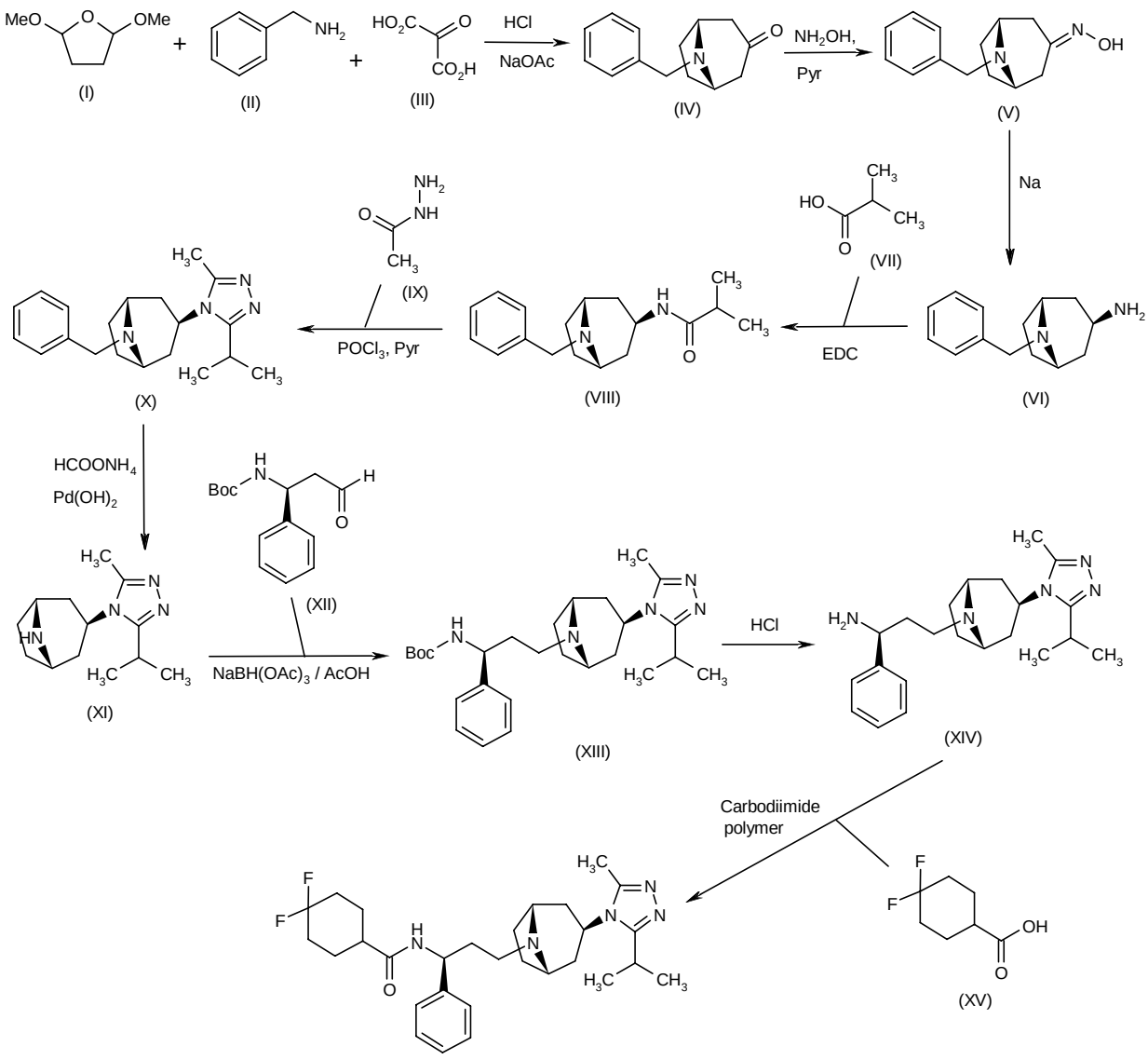
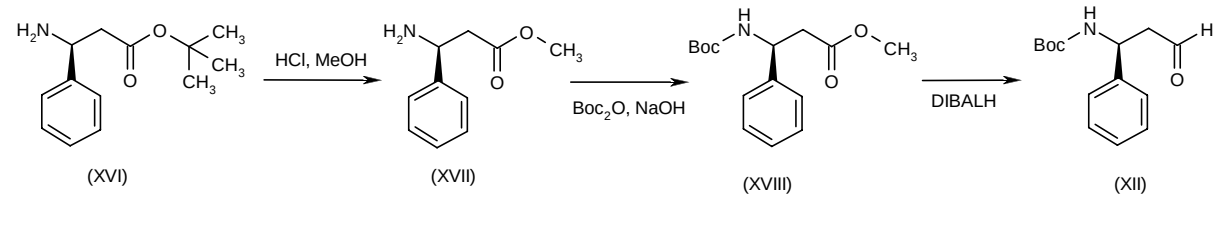
Scheme 1: Synthesis of Maraviroc



Scheme 2: Synthesis of Intermediate (XII)



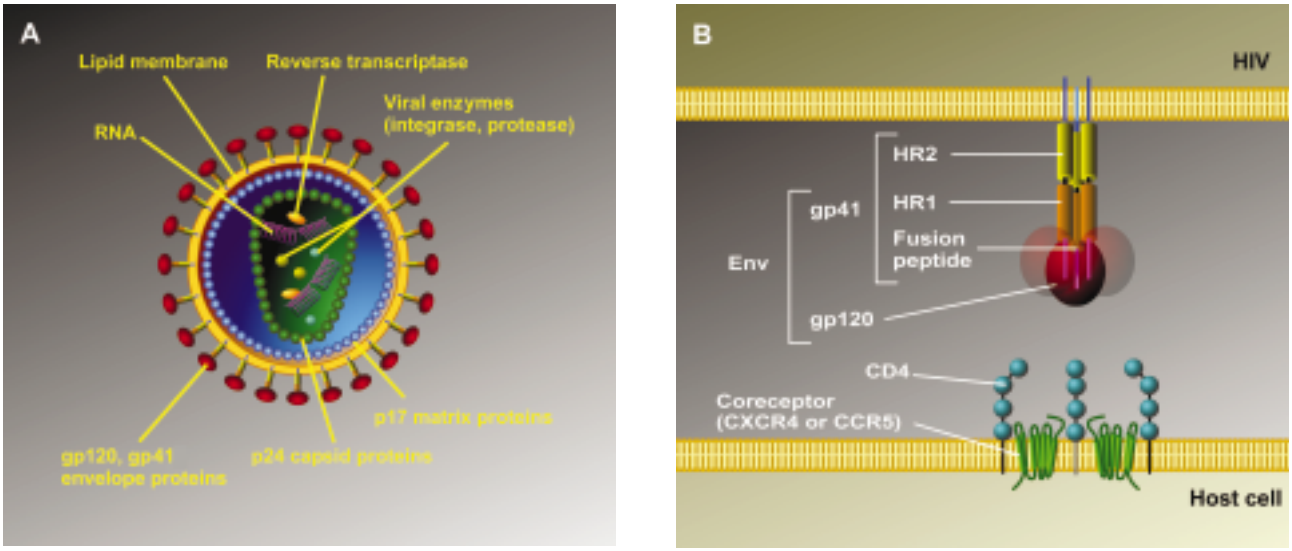


Fig. 1. **A:** HIV nucleocapsid contains 2 copies of a positive sense single-stranded RNA and 2 copies of the reverse transcriptase, together with other viral proteins. The capsid is in turn enclosed in a layer of matrix protein, which is associated with a lipid bilayer or envelope containing the proteins 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 coreceptor (*i.e.*, CCR5, CXCR4). Animations are available on the Prous Science LifeSciChannel.

antiretroviral therapy (ART) based on combinations of antiviral drugs targeting reverse transcriptase (RT) and protease (PR) altered the natural history of the infection and reduced the associated mortality and morbidity. However, patient adherence to treatment, drug interactions, toxicity, adverse events, viral resistance and the generation of reservoirs remain major problems that limit the efficacy of treatment combinations. Thus, new antiviral drugs targeting different steps in the replicative cycle of HIV are needed.

HIV entry is considered an attractive target for chemotherapeutic intervention. The blockade of this first step in the HIV life cycle leads to suppression of viral infectivity, replication and cytotoxicity induced by virus-cell contacts. HIV enters target cells by a sequential process. The first event is attachment of the virus to the T-cell surface, followed by binding of the trimeric envelope complex to the CD4 receptor through the gp120 envelope glycoprotein. This promotes conformational changes in gp120 that unmask the coreceptor binding site and allow for the interaction between the CD4-envelope glycoprotein complex and the appropriate chemokine receptor, mainly CXCR4 (X4 virus) or CCR5 (R5 virus) *in vivo*, used as a coreceptor. Finally, in response to such coreceptor binding, there are additional conformational changes that allow pore formation and fusion of virus and cell membranes, both mediated by the gp41 envelope glycoprotein (3) (Figs. 1 & 2).

The first drug inhibiting HIV entry approved by the Food and Drug Administration (FDA), the fusion inhibitor enfuvirtide (T-20, Fuzeon™) (4), targets this last step. However, a number of compounds are being developed to specifically target other parts of the process (gp120-CD4 binding inhibitors and chemokine receptor antagonists), and some of them, mainly CCR5 antagonists, have reached early clinical trials (Table I). CCR5 is a particularly attractive target because it is a G-protein-coupled receptor, classically a good target to develop selective, low-dose, bioavailable drugs, and its function seems dispensable (individuals who do not express the receptor due to a 32-amino-acid deletion in the gene encoding CCR5 are healthy). CCR5 antagonists inhibit infection by R5 strains, the major viral species transmitted and present throughout the disease. In contrast, they are not expected to have an effect on either the more pathogenic X4 strains, which appear in 50% of cases in late disease and are associated with a more rapid progression, or the so-called dual-tropic strains (R5X4), which are able to utilize both coreceptors but predominantly use CXCR4 *in vivo*. To date, there are no approved drugs in this family of inhibitors (3).

Maraviroc (UK-427857) is one such compound which has shown promising early results during its development, and Pfizer recently advanced it into phase III clinical trials for the treatment of HIV-infected subjects.

Pharmacological Actions

Maraviroc is a potent, specific, noncompetitive CCR5 receptor antagonist that inhibits the binding of HIV gp120 (IC_{50} = 43 nM) and the endogenous ligand for the coreceptor MIP-1β (IC_{50} = 3-7 nM). This agent binds the receptor reversibly but with a long half-life, which may confer advantageous pharmacodynamics. Maraviroc inhibits HIV entry into target cells and displays potent

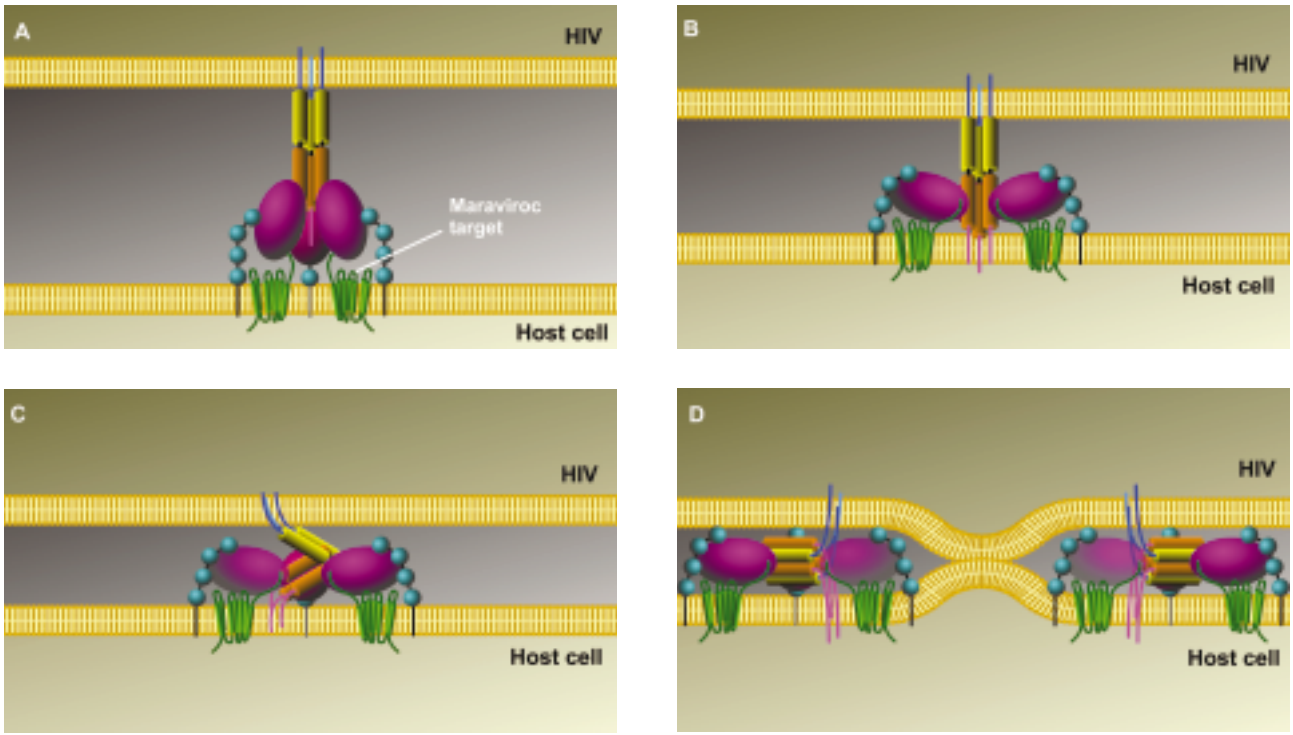


Fig. 2. **A:** Binding of viral gp120 to CD4 induces the first conformational change in gp120 that unmasks the coreceptor binding site. Maraviroc binds to CCR5 such that HIV cannot successfully bind with the coreceptor, thus preventing viral entry and infection. **B:** Binding of gp120 to the coreceptor induces the second conformational change in gp120, in response to which the fusion peptide inserts in the host cell membrane. **C:** HR1 and HR2 form a 6-helix bundle. **D:** This juxtaposes the viral and cellular membranes, resulting in pore formation and membrane fusion. Animations are available on the Prous Science LifeSciChannel.

antiviral activity against a wide range of primary HIV isolates, recombinant viruses derived from both antiretroviral drug-sensitive and -resistant clinical isolates, and laboratory strains across multiple clades (IC_{90} < 10 nM), all using CCR5 for entry, while exhibiting no activity against X4 or R5X4 isolates and no cytotoxicity at up to 10 μM. Its *in vitro* activity does not appear to be affected by different viral multiplicities of infection (MOIs), donor-to-donor variations in peripheral blood mononuclear cells (PBMCs) or removal of monocytes (5-7).

Maraviroc does not bind to mouse, rat or dog CCR5 homologues but has a strong and similar binding affinity for both macaque and human CCR5 receptors, and functional antagonist activity at the macaque receptor (8).

It has been extremely difficult to elicit *in vitro* resistance to maraviroc. This was obtained following prolonged serial passage of primary virus in culture in the presence of increasing drug concentrations, although resistance developed in only 3 of 6 strains after 14 weeks. In one case, a strain switched from using CCR5 to CXCR4 for entry. Also, one of the resistant strains showed reduced infectivity compared to the parent virus (9). Since previous studies showed that all small-molecule CCR5 inhibitors interacted with a similar region of the receptor, a pocket formed by the transmembrane helices and the extracellular loop 2 (ECL2), the idea of generalized class resistance was suggested. However, a recent study showed that CCR5 antagonists with similar structures but different key functional groups (triazole *vs.* imidazopiperidine) display differential activities against maraviroc-resistant primary isolates. This finding raises the possibility that resistance to a coreceptor antagonist will not necessarily lead to drug class resistance (10).

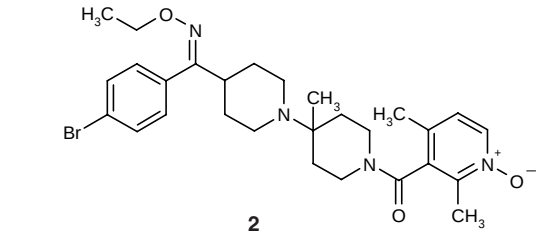
Pharmacokinetics

Maraviroc is orally bioavailable in humans. Preclinical pharmacokinetic studies showed that the drug has a favorable pharmacokinetic profile, although its physicochemical properties (moderately lipophilic and basic, with a number of H-bonding functionalities and a molecular weight of 514) make it borderline for such a good profile.

Drug disposition studies performed in dogs and rats administered maraviroc intravenously showed a moderate to high clearance and a large volume of distribution, with respective half-lives of 2.3 and 0.9 h; 12% of the dose was recovered in urine in dogs. Oral bioavailability in dogs and rats was 41% and 6%, respectively, with absorption estimated to be approximately 20-30% in rats and > 70% in dogs. In rats, drug levels in cerebrospinal fluid (CSF) were 10% of the free plasma levels after i.v.

Table I: HIV entry inhibitors targeting CCR5 under active development for the treatment of HIV infection.

Drug name	Phase	Source
1. AMD-887*	Preclinical	AnorMED
2. Ancriviroc	Phase I	Schering-Plough
3. SCH-D	Phase I	Schering-Plough
4. TAK-220	Phase I	Takeda
5. TAK-652	Phase I	Takeda
6. 873140/Ono-412	Phase II	GlaxoSmithKline; Ono
7. Maraviroc	Phase III	Pfizer



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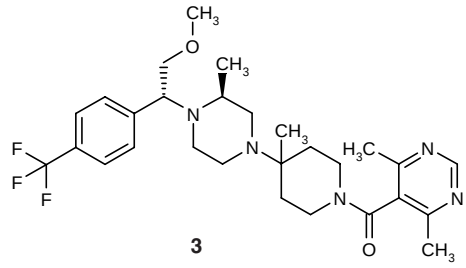

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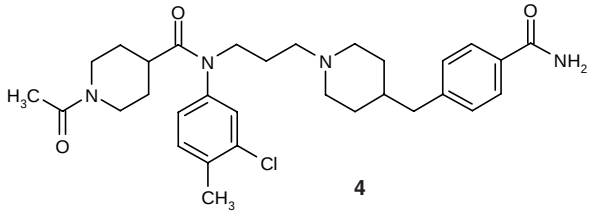

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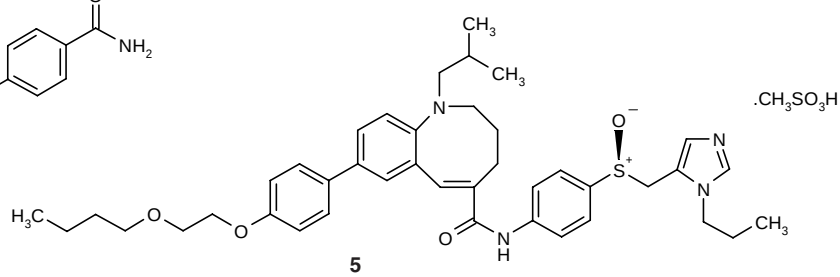

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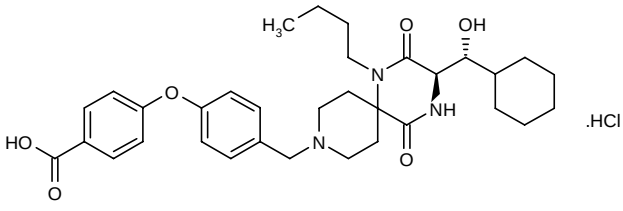

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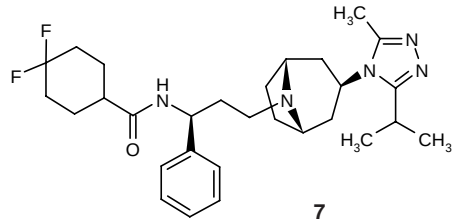

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*Chemical structure not yet detected.

infusion. Studies in Caco-2 cells showed that maraviroc had poor membrane permeability and that inhibitors of P-glycoprotein augmented its transcellular flux. Further evidence for a role for P-glycoprotein-mediated efflux in restricting the absorption of maraviroc was obtained in P-glycoprotein knockout mice, in which systemic exposure (AUC) was higher compared to control animals (11, 12).

In humans, orally administered maraviroc displayed a nonlinear pharmacokinetic pattern: increasing doses were associated with superproportional increases in dose-normalized exposure, suggesting P-glycoprotein saturation. This was not observed in either dogs or rats, probably because the drug did not bind to the CCR5 receptor of these species. Although some metabolism of the drug was observed in both humans and animals, the parent compound was the only significant component in circulation, urine and feces after oral administration. In rats, it was secreted directly into the gastrointestinal tract via the bile. Metabolites were similar in all species and resulted from oxidative reactions (12).

In a phase I study conducted to evaluate the pharmacokinetics of maraviroc, healthy male volunteers were orally administered placebo or single (1-1200 mg) or multiple doses (3-300 mg b.i.d. and 600 mg once daily for 12 days) of the drug. Absorption was rapid and maximum plasma concentrations were reached between 0.5 and 4 h after dosing. For doses of 100 mg or more, the pharmacokinetic profile was dose-proportional. Maraviroc exhibited both a long terminal half-life following multiple dosing (around 17 h) and slow receptor dissociation. A dose of 100 mg b.i.d. resulted in plasma concentrations above the *in vitro* antiviral IC_{90}. However, the drug showed a decreased rate and extent of absorption with food intake. Maraviroc was well tolerated at the doses studied (13).

Since maraviroc will be given in combination with other antiretroviral drugs, several open, randomized,

placebo-controlled, crossover studies evaluated drug interactions with other HIV treatments. In one of these, 11 healthy volunteers enrolled received maraviroc 300 mg b.i.d. with tenofovir 300 mg once daily or placebo for 7 days. No significant differences in maraviroc AUC or C_{max} were seen with tenofovir as compared to placebo treatment, indicating that there was no significant drug interaction (14). In another study, coadministration with protease inhibitors was assessed in 12 healthy subjects given maraviroc 300 mg b.i.d. and atazanavir 400 mg once daily on days 1-7 and then maraviroc with atazanavir 300 mg plus ritonavir 100 mg on days 8-14. Control treatment consisted of maraviroc 300 mg b.i.d. plus placebo. Atazanavir increased maraviroc exposure, which was further increased with the addition of ritonavir. The results suggested that doses of maraviroc should be reduced when given in combination with protease inhibitors (15). Finally, in a study involving coadministration with P-450 CYP3A4 inhibitors in 36 healthy volunteers, the AUC and C_{max} values for maraviroc (300 mg b.i.d.) increased 3.9- and 2-fold, respectively, after 7 days of coadministration with lopinavir/ritonavir (400/100 mg b.i.d.). The increases were attenuated when efavirenz (600 mg once daily) was added to combined treatment. Saquinavir/ritonavir (1000/100 mg b.i.d.) also increased maraviroc AUC and C_{max} values by 9.8- and 4.7-fold, respectively. Efavirenz again reduced these increases by approximately half (16).

Drug interactions between maraviroc and other anti-HIV drugs were also investigated in patients who had been stable for at least 3 months on common antiretroviral treatments (17). Regimens containing efavirenz (efavirenz + lamivudine/zidovudine and efavirenz + didanosine + tenofovir) affected maraviroc pharmacokinetics, resulting in approximately a 50% reduction in drug exposure compared to previous studies with 10-day monotherapy. A nevirapine-containing regimen (nevirapine + lamivudine + tenofovir) only slightly increased C_{max} and had no effect on AUC, while a lopinavir/ritonavir (Kaletra™)-containing regimen (Kaletra™ + stavudine + lamivudine) approximately doubled drug exposure. These observations confirmed those previously seen in healthy subjects and support the idea that maraviroc doses have to be adjusted depending on background treatment.

Toxicity

The selectivity of maraviroc for the human CCR5 receptor was confirmed and, in rodents, no effects on the central or peripheral nervous, renal and respiratory systems, hemodynamic parameters or cardiac repolarization were observed at concentrations largely exceeding the IC_{90} (11).

A preclinical study evaluated the potential effects of maraviroc on cardiac repolarization through inhibition of the hERG (human ether-a-go-go-related gene) potassium (K^+) channel, a component of the rapidly activating delayed rectifier K^+ channel ($K_{V(r)}$) (18). *In vitro* interaction with this channel and effects on action potential in isolated canine Purkinje fibers and on Q-T intervals *in vivo* in a dog model were measured. Maraviroc was found to be a weak inhibitor of the hERG channel, as concentrations above 3 μM inhibited the binding of dofetilide, a selective hERG ligand, and potassium current using the human recombinant channel, and increased the cardiac action potential duration. Moreover, maraviroc had no effect on the Q-T interval after oral administration to dogs at free drug concentrations in plasma > 100-fold higher than the IC_{90} for inhibition of HIV-1 replication. Since maraviroc has been shown not to bind to the CCR5 receptor in the dog, the results from this study suggested that any effect on the Q-T interval also observed with other CCR5 antagonists is not necessarily related to blockade of this receptor.

The favorable cardiac safety profile of maraviroc was further confirmed in a randomized, placebo-controlled, crossover clinical trial that found no clinically significant effects on cardiac repolarization in 61 healthy subjects treated with single doses of maraviroc (100, 300 or 900 mg) and moxifloxacin (400 mg). A mean difference in $Q\text{-}T_c$ intervals of < 4 ms compared to placebo was found for all maraviroc doses compared to the increase of 12-14 ms following moxifloxacin. $Q\text{-}T_c$ interval values did not increase more than 60 ms from baseline in any of the maraviroc-treated patients and none showed maximum values of > 450 ms for males or > 470 ms for females. No serious adverse events were reported, the most common being dizziness at the highest dose, although headache, postural hypotension, nausea and cystitis were also reported (19). The results from this and several of the following clinical safety and efficacy studies are depicted in Table II.

The safety of maraviroc was also examined in a double-blind, placebo-controlled study in 54 healthy males and females given multiple doses of the drug (100 or 300 mg b.i.d.) or placebo for 28 days. Again, the drug was well tolerated, with no effects on laboratory measurements (hematology, clinical chemistry and lipid profiles), electrocardiogram, blood pressure or heart rate, and no serious adverse events reported (20).

Maraviroc was also safe and well tolerated in young women in another study with the primary objective of determining the effect of the drug on the pharmacokinetics of oral contraceptive steroids, which were not altered (21).

Clinical Studies

A study to evaluate the effect of short-term (10 days) monotherapy with maraviroc (100 mg b.i.d. or 25 mg once daily) compared to placebo was performed in 24 asymptomatic HIV-positive patients prescreened for infection with R5-tropic virus (22). The drug achieved plasma drug concentrations comparable to those seen in healthy subjects (13) and levels at the dose of 100 mg b.i.d. exceeded the mean antiviral IC_{90} in all patients. Mean saturation

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind Crossover	Maraviroc, 100 mg Maravirov, 300 mg Maraviroc, 900 mg Moxifloxacin, 400 mg Placebo	61	Maraviroc had no significant adverse effects on the Q-T_c interval of healthy volunteers	18
Healthy volunteers	Randomized Double-blind	Maraviroc, 100 mg b.i.d. x 28 d Maraviroc, 300 mg b.i.d. x 28 d Placebo	54	Maraviroc was well tolerated and mostly associated with mild adverse events when given to healthy volunteers for 28 days	19
Healthy volunteers	Crossover	Maraviroc, 100 mg b.i.d. x 11 d + on d 2-8 Placebo + Ethinylestradiol, 30 μg p.o. o.d. + Levonorgestrel, 150 μg p.o. o.d. on d 2-8	15	Maraviroc was well tolerated and induced no clinically significant changes in laboratory values, electrocardiogram parameters, blood pressure or heart rate in healthy female volunteers	20
HIV infection		Maraviroc, 25 mg o.d. x 10 d Maraviroc, 100 mg b.i.d. x 10 d Placebo	24	Maraviroc was safe and dose-dependently reduced viral load in patients with HIV infection	21
HIV infection	Randomized Double-blind	Maraviroc, 25 mg o.d. x 10 d Maraviroc, 50 mg b.i.d. x 10 d Maraviroc, 100 mg o.d. x 10 d Maraviroc, 100 mg b.i.d. x 10 d Maraviroc, 150 mg b.i.d. x 10 d Maraviroc, 300 mg o.d. x 10 d Maraviroc, 300 mg b.i.d. x 10 d Placebo	80	Maraviroc at doses up to 300 mg b.i.d. was well tolerated and reduced the viral load of HIV-infected patients	23
HIV infection	Randomized Double-blind	Maraviroc, 25-600 mg/d x 10 d Placebo	79	Maraviroc was more effective than placebo in reducing the viral load of HIV-infected patients	24

of CCR5 was > 90% during the 10 days of treatment with 100 mg but fell to < 80% at the lowest dose. Patients bearing CCR5-using viruses and treated at the highest dose achieved a mean decrease in viral load of 1.42 $\log_{10}$ from baseline to day 11, whereas those given the dose of 25 mg once a day showed a reduction of 0.42 $\log_{10}$. No serious adverse events were reported.

In a phase IIa trial, a patient harboring viruses with a dual-tropic phenotype who was erroneously selected to participate was analyzed to search for correlates of maraviroc efficacy. The relationship between pharmacodynamics and pharmacokinetics with changes in the circulating viral populations was also studied (23). This patient did not respond to maraviroc although normal pharmacokinetic and CCR5 saturation profiles were obtained. R5 strains, the majority at baseline, were sensitive to the drug *in vitro* and thus were selectively suppressed by treatment, leading to predominance of CXCR4-using variants. This was reversible since R5 again represented the majority after stopping the treatment, indicating that the CCR5 antagonist does not induce a permanent change in coreceptor use.

In another monotherapy study to evaluate drug dosing frequency and the effect of food in HIV-infected individuals, viral load reduction, pharmacokinetic and pharmacodynamic parameters were assessed in 80 patients treated over 10 days with maraviroc or placebo (24). The drug was well tolerated at all doses administered (25, 100 and 300 mg once daily and 50, 100, 150 and 300 mg b.i.d.) and similar dose-dependent reductions in viral load were observed with both once- and twice-daily dosing (0.43, 1.13 and 1.35 $\log_{10}$, respectively, for doses of 25, 100 and 300 mg once daily, and 0.66, 1.42, 1.45 and 1.6 $\log_{10}$, respectively, for 50, 100, 150 and 300 mg b.i.d.). Plasma drug levels were similar to those seen in healthy volunteers under similar conditions (13). In an additional experiment, administration of maraviroc 150 mg b.i.d. with a high-fat meal did not affect antiviral efficacy.

Mathematical modeling was used to describe the efficacy of short-term maraviroc monotherapy in 79 patients receiving doses of 25-600 mg/day or placebo for 10 days. The model showed that the rate of viral load decline was similar to that seen with potent protease inhibitor monotherapy but slower than with combination therapies. Greater viral load reductions were found with higher doses, and a dose of 100 mg b.i.d. or higher was recommended for evaluation in long-term studies of combination therapy (25).

Apart from resistance, a concern with the use of CCR5 antagonists for HIV therapy is the possible emergence of more pathogenic X4 variants during treatment. Dual-tropic viruses were found after 10-day maraviroc monotherapy in 2 of 65 patients initially carrying only R5 virus. However, analysis of HIV envelope sequences from both patients revealed that CXCR4-using virus most likely emerged from a pretreatment dual-tropic reservoir

rather than from a change in coreceptor use following treatment with the CCR5 antagonist (26).

Phase III clinical trials with maraviroc were recently initiated (27).

Source

Pfizer, Inc. (US).

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