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Chemokine Receptor CCR5 Antagonist Maraviroc: Medicinal Chemistry and Clinical Applications

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Abstract

The human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS), one of the worst global pandemic. The virus infects human CD4 T cells and macrophages, and causes CD4 depletion. HIV enters target cells through the binding of the viral envelope glycoprotein to CD4 and the chemokine coreceptor, CXCR4 or CCR5. In particular, the CCR5-utilizing viruses predominate in the blood during the disease course. CCR5 is expressed on the surface of various immune cells including macrophages, monocytes, microglia, dendritic cells, and active memory CD4 T cells. In the human population, the CCR5 genomic mutation, CCR5 $\Delta 32$, is associated with relative resistance to HIV. These findings paved the way for the discovery and development of CCR5 inhibitors to block HIV transmission and replication. Maraviroc, discovered as a CCR5 antagonist, is the only CCR5 inhibitor that has been approved by both US FDA and the European Medicines Agency (EMA) for treating HIV/AIDS patients. In this review, we summarize the medicinal chemistry and clinical studies of Maraviroc.

Keywords

Antiretroviral therapy; Clinical study; HIV-1; HIV-2; Medicinal chemistry; Microbicide; SAR

Introduction

The human immunodeficiency virus (HIV) infection leads to acquired immunodeficiency syndrome (AIDS), which afflicts an estimated 35.5 million people globally. HIV enters the host cells through the fusion of the lipid membrane of the virus with that of the host cells. The fusion is triggered by the interaction of the viral surface protein (gp120) with specific host cell surface receptors, CD4 and the chemokine coreceptor CXCR4 or CCR5 [1–9].

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Conflict of Interest:

Declared none.

The importance of the chemokine coreceptors in HIV infection and pathogenesis has been demonstrated by the findings that a mutant allele of the CCR5 gene, CCR5-Δ32, confers relative resistance to HIV infection [10]. CCR5 is expressed on the surface of various immune cells including macrophages, monocytes, microglia, dendritic cells, active memory CD4 T cells. Given the natural existence of CCR5 deletion in the human population, it is feasible to target CCR5 to block HIV infection. Therefore, the development of CCR5 antagonists has become a high research priority in recent years.

Maraviroc is a CCR5 antagonist that inhibits the entry of HIV into host cells by blocking gp120 interaction with CCR5 [11]. Currently, Maraviroc is the only CCR5 inhibitor that has been approved by both US FDA and the European Medicines Agency (EMA) for the treatment of antiretroviral drug-experienced and -naïve patients [12, 13]. The approval of Maraviroc for clinical use was based on the Maraviroc plus Optimized Therapy in Viremic Antiretroviral Treatment Experienced patients (MOTIVATE) 1 and MOTIVATE 2 studies [14]. In this review, we mainly focus on the medicinal chemistry of Maraviroc and its recent clinical applications in combination with other antiretroviral drugs. We also review the development of Maraviroc as an anti-HIV microbicide.

1. Medicinal Chemistry of Maraviroc

Maraviroc (Figure 1) was discovered in 2005 by Pfizer global research and development team. It was identified through the combination of high-throughput screen (HTS), high throughput binding assay, and medicinal chemistry [15].

It took approximately two and a half years of development from the initial high throughput screening, during which 965 analogues were synthesized through medicinal chemistry. Maraviroc was finally identified with the desirable antiviral activity, metabolic stability, absorption, and hERG inhibition. It took another two more years of clinical studies to have Maraviroc approved by FDA for the treatment of HIV/AIDS. Currently, research is still ongoing to develop Maraviroc-related analogues with improved pharmacokinetics. In the following section, we review the medicinal chemistry in the discovery of Maraviroc and Maraviroc-related analogues.

1.1 Discovery of Maraviroc

In the discovery of Maraviroc, nearly 1,000 analogues were synthesized, from which Maraviroc emerged as the best drug candidate [16, 17]. Several important steps leading to the identification of Maraviroc have been taken:

1.1.1 Identification of the hits and the lead compounds—A chemokine radioligand-binding assay was first used to screen the Pfizer compound library to identify small-molecule CCR5 ligands. A number of hits were identified from the HTS and then triaged. Four hits remained in the pool after taking into account of target affinity, ligand efficiency, and toxicity. Then, two of them, the imidazopyridine **1** (UK-107,543) (MIP-1β IC₅₀ 0.4 μM) and **2** (UK-179,645) (MIP-1β IC₅₀ 1.1 μM) (Figure 2), were chosen as the start points of an intensive medicinal chemistry program for further optimization [15].

However, neither of the two hits could be considered as the lead compound because of the lack of desirable properties such as a low molecular weight, high binding affinity, and potent antiviral activity. Therefore, hit-to-lead studies were taken as the second step.

To develop the lead compound, the most attractive features of the two hits were combined to produce novel and selective antagonists, in which compound **3** became the focus of the structure-activity relationship (SAR) investigations. Compound **3** exhibited good chemokine receptor binding (MIP-1 β IC₅₀ 45 nM) and antiviral activity. SAR studies of different amide substituents were firstly started. SAR suggested that the amide substituent interacts with a predominantly lipophilic binding site in the CCR5 receptor, and the cyclobutyl amide analogue **4** was the most potent one in this series (Table 1). Further studies established the (*s*) enantiomer of cyclobutyl amide (*s*)-**4** was the active isomer. Then, starting from compound (*s*)-**4**, by keeping the cyclobutyl substituent constant, a series of piperidine analogues were generated, among which, the tropane derivatives **5** and **6** (exo and endo isomers) were found to be highly potent inhibitors of viral replication. The piperidine ring in **6** was forced into a boat conformation, the resulting structure overlaps well with that of the exo substituted analogues. Compound **5** possessed the enhanced binding affinity and improved antiviral activity than the two hit compounds, and it was also a potent ligand for the hERG channel, displaying 80% inhibition of the binding of tritiated dofetilid when screened at 300 nM. The endo isomer **6** was essentially equipotent to **5**. They were chosen as lead compounds for further optimization.

1.1.2 Lead Optimizations—In the development of Maraviroc, Price et al focused on hERG liability and used the [³H]-dofetilide binding assay to enable critical SAR analysis [16, 17]. They started with the lead compound **5**, which was a potent ligand for the CCR5 receptor and also a potent ligand for the hERG channel. The study on the compound **7** with the oxygen bridgehead having a profound effect on the basicity of the nitrogen demonstrated that the change of the basicity/steric environment of the central nitrogen atom has had little effects on the compounds' affinity for the hERG channel (Table 2). So they decided to focus on the optimization of benzimidazole moiety [16, 17].

Docking of compound **5** into the model of hERG channel indicates that the phenyl group of the benzimidazole overlaps perfectly with a lipophilic binding area, which suggested alternative expressions for the benzimidazole would reduce affinity for the hERG channel. Complete replacement of the benzimidazole rather than modification was chosen as the best strategy. Compound **8** was found to have good levels of antiviral potency but with some increased affinity for the hERG channel compared to compound **5**. It was found that the affinity for the hERG channel had started to return with increased lipophilicity in this series, and the triazole series showed a superior profile to the benzimidazole [16, 17].

Based on the model of the hERG channel, modification of the cyclobutyl amide turned to reduce the affinity for the channel. After parallel chemistry in the final step amide coupling, this work was rapidly performed, and within the triazole series, the 4,4-fifluorocyclohexyl group showed no activity for the hERG channel due to the steric demands of the cyclohexyl group and the dipole generated by the difluoro moiety. Eventually, Maraviroc was discovered with potent antiviral profile and lack of affinity for the hERG channel.

Maraviroc possesses excellent antiviral potency, reasonable microsomal stability, high selectivity over potential ion channel effects, good aqueous solubility, and no significant binding to the HERG potassium channel at 1,000 nM.

To summarize, rapid ability to generate high quality data in a well validated assay and excellent pharmacophore models of the hERG channel eventually led to the discovery of Maraviroc [16, 17].

1.2 Maraviroc-related analogues

Maraviroc contains a tertiary amine (tropane), two hydrophobic groups, and one heteroaryl group, and these four pharmacophore elements are found in most CCR5 antagonists.

1.2.1 Tertiary amine (tropane) analogues—The tropane bridge often gave a potent activity in cell-based gp160 fusion assay, and was proved beneficial for antiviral activities due to steric hindrance around the central basic center and restrained conformational flexibility of the molecule [15]. For example, the antiviral activity was lost when the bridge was removed from Maraviroc to give **9** [18]. (Table 3)

Barber et al. proposed that similar steric hindrance and conformational effects could also be achieved through the addition of an alpha methyl branch onto the 3-amino-3-phenyl-propyl side chain. For example, removal of the tropane bridge and the ethyl substituent from compound **10** to give **11** resulted in a loss of fourfold in potency. However, the alpha-methyl derivative **12** increased the potency about threefold over the equivalent tropane **10** [18] (Table 3). With further exploration and SAR studies on the 4-position of piperidine of **12**, replacement of the tropane core of maraviroc by piperidine with a branched *N*-substituent yielded a new class of CCR5 antagonist [18], among which compound **13** and **14** with 1,3,4-triazoles showed good whole cell antiviral activity, metabolic stability, and in the case of **13**, only weak activity at the hERG ion channel (Table 4). Further investigation is ongoing for this series of compounds.

Lemoine et al [19] evaluated the effects of replacement of 3-amino-8-azabicyclo [3.2.1] octane in Maraviroc. The tertiary amine as part of the rigid 8-azabicyclo [3.2.1] octane bicyclic system was replaced with the 5-amino-3-azabicyclo[3.3.0] octane. The pKa values of the tertiary amine of the 4-substituted dimethyl 1,2,4-triazole derived from 3-aminotropane, and that derived from the bicyclic exo or endo 5-amino-3-azabicyclo[3.3.0] octanes were calculated to be virtually the same (9.47 ± 0.48 , 9.42 ± 0.48 , respectively), and the only difference between the two ring systems would be structural and conformational [19]. Then, a series of compound **15** in both sub-series (exo or endo) were prepared to study the replacement effects, by comparing to the series of compound **16** with the tropane core (Figure 3).

It was concluded that the bicyclic exo and endo 5-amino-3-azabicyclo[3.3.0] octanes were effective but not equal replacements for the conformationally restricted tropane in Maraviroc (Table 5) [19].

More SAR exploration would be needed for further optimization of both the endo and the exo-sub-series, however no other compounds were reported in this new series, likely because of the decreased potency in comparison with Maraviroc.

1.2.2 Tropane core retained analogues

1.2.2.1 N-ethyl spacer analogues: Ernst and coworkers identified compound **17**, which contained the attractive features of reported templates, including those from maraviroc [20]. From the starting compound **17** ($IC_{50} = 0.97 \mu M$), the N-ethyl spacer was elongated by one carbon to give a compound **18** which showed three fold higher potency ($IC_{50} = 0.31 \mu M$). Modification of the cyclohexylamide moiety of **18** to a urea resulted in compound **19** with a 10-fold increase in potency (Table 6).

Then, the SAR studies of compound **19**, containing two different features, elongated N-ethyl spacer and urea functionality instead of amide functionality compared to Maraviroc, were done through introduction of different urea derivatives, modifications of the triazole moiety, and introduction of fluorine atom to the phenyl ring. Representative compounds are summarized in Table 6 and 7. The data showed the para-substituted phenyl urea group gave high potency in chemokine binding assay, and the series of compounds were represented by compound **20** (Table 6). Incorporation of a polar side chain to triazole moiety in an appropriate orientation improved the viral entry inhibition potency, and compound **21** possessed potent antiviral activity after triazole was replaced with imidazole. *Meta*-Fluoro-substitution at the phenyl ring of **22** appeared to be tolerated to the viral entry inhibition, however, *para*-fluoro-substituted analogue **23** just retained one tenth of potency compared to compound **21**. With these modifications, a series of substituted imidazopiperidine-tropane CCR5 antagonists were yielded, and the antiviral properties were optimized through a luciferase-reporter phenotypic viral entry assay [21]. Compound **24** was identified with attractive pharmacokinetic, selectivity, and antiviral properties. Further studies with **24** are ongoing [20].

1.2.2.2 Hydrophobic group analogues: Through robust chemical approaches toward putative CCR5 antagonist scaffolds and evaluation of analogues in the ^{125}I -[MIP-1 β] binding and Ba-L-Hos antiviral assays, a series of 4,4-disubstituted piperidine-based CCR5 antagonists were discovered [22, 23]. Among them, compound **25** and **26** showed high potency and bioavailability (Table 8), which were used as lead molecules for further optimization. Through hERG and pharmacokinetics SAR studies, a druglike compound **27** was obtained with improved potency and bioavailability [24].

By replacing the piperidine ring of 4,4-disubstituted piperidine-based CCR5 antagonists with cyclohexylamine (Figure 4), a series of 4,4-disubstituted cyclohexylamine based CCR5 antagonists were developed.

SAR studies were done on the linker and amide moiety indicated in Figure. A representative compound **28** (Figure 5) was obtained with pronounced activity against HIV-1 (HOS $IC_{50} = 58 \text{ nM}$) [25].

1.2.2.3 Heteroaryl analogues: Maraviroc is dosed b.i.d. clinically and has moderate bioavailability in man with food effects on oral exposure [26, 27]. To address this, a new series of imidazopiperidine CCR5 antagonists were developed, and they retained the antiviral profile and hERG activity of Maraviroc [28]. Moreover, they possessed improved absorption profiles in rat and dog. In the development of the new series of CCR5 antagonists, the medicinal chemistry started with lead compound **29** (Figure 6). As a lead compound, **29** had several important features. For examples, the acetyl of the amide moiety of **29** minimizes the lipophilic interactions to a lipophilic region of the hERG pharmacophore, and therefore reduced affinity to the hERG channel; the tropane core, retained the same as Maraviroc, ensured excellent antiviral activity and overcame problems such as CYP inhibition [11]; the benzimidazole retained compound **29** with potent activity in the gp160 fusion assay and moderate activity in a hERG binding assay. Similar to the SAR study strategies used by Ernest et al, the benzimidazole moiety of **29** was converted to imidazolepiperidine for the increased polarity, the fluorine atom was introduced to the meta position of phenyl ring for the improved Caco-2 profile. Then, a series of imidazolepiperidine and isomeric imidazolepiperidine CCR5 antagonists were developed, among which **30** (PF-232798) was screened with complete oral absorption in rat and dog and demonstrated improvement for in vitro metabolic stability in comparison with Maraviroc (Table 9). Compound **30** has shown improvement for in vitro metabolic stability and antiviral activity against HIV BaL in PBMCs in comparison with Maraviroc. Furthermore, compound **30** retained antiviral activity against a Maraviroc-resistant HIV-1 strain. Thus, compound **30** was chosen for further clinical studies, based on a favorable profile in preclinical safety studies. Phase II clinical studies of compound **30** are ongoing [28].

1.2.2.4 Maraviroc-hybrid molecules: A series of small molecule CCR5 antagonists were designed and synthesized through fragment assembly, based on the structures of Maraviroc and the compound **31** (Figure 7), which was identified through structure-based virtual screening. Representative Compound **32** (Figure 7) had an IC₅₀ value of 0.233 μ M [29]. Preliminary SARs showed that the 4,4-difluorocyclohexanecarbonyl is important to maintain the antagonistic activity, and the activity could be significantly different with different heterocyclic aryl groups. Although this series of compounds did not show more potent activity compared with Maraviroc, the novel scaffold could be applied in the development of Maraviroc-derived second generation of CCR5 antagonists [29].

To summarize, among those Maraviroc-related analogues, compound **30** (PF-232798) is under clinical phase II study, and **27** (GSK 163929) has completed with the preclinical characterization, and further progression to the clinic is ongoing. The SAR in the development of Maraviroc and its analogues may provide useful information in the discovery of other drugs for the treatment of HIV.

2. Clinical studies

Maraviroc blocks the binding of gp120 to CCR5 receptor selectively and reversibly. This interaction prevents the conformational changes necessary for the M-tropic HIV entry into host cells [15]. Maraviroc has been a drug to treat HIV/AIDS in the market for several years, and the clinical studies have been continuing, and had been reviewed previously [13, 30–

33]. Here, we mainly focus on recent clinical applications of Maraviroc in combination with other antiretroviral drugs and as an anti-HIV microbicide.

2.1 Determination of HIV tropism

Maraviroc is effective to prevent the R5-tropic viruses to enter the cell, however, X4 or dual/mixed populations are unaffected by the drug. It is necessary to determinate the viral tropism prior to initiating therapy.

Before prescribing Maraviroc, it is mandatory to determine viral tropism. In current clinical practice, Trofile[®] and its new version (ES-Trofile[®]) assays are predominantly performed. Genotypic methods are developing in Europe as an alternative to ES-Trofile[®] [34]. Maraviroc clinical test (MCT) is a clinical approach to determine the treatment with Maraviroc. MCT could be considered as an additional method before CCR5-antagonist prescription, since the rate of the virological success increased in a combined antiviral therapy after MCT [35].

2.2 Pharmacokinetics

The pharmacokinetics of Maraviroc was evaluated when administered at 150 mg once daily in combination with lopinavir/ritonavir in HIV-positive treatment-naïve patients [36]. Lopinavir and ritonavir exposure were not affected by the coadministration of Maraviroc, and all PK values were comparable to what was previously reported. The study showed that 150 mg dosing of Maraviroc once daily compared to twice daily seems to be pharmacologically enough [36].

The pharmacokinetic profile of a novel nucleoside-sparing combination antiretroviral regimen, which is an attractive option for the treatment of HIV infection, was established by Mora-Peris and the coworkers [37]. Eligible participants were the HIV-infected subjects on stable once-daily antiretroviral therapy receiving 245/200 mg of tenofovir/emtricitabine plus 800/100 mg of darunavir/ritonavir. Maraviroc once daily was added to the current combination antiretroviral therapy during study period 1 (days 1–10), tenofovir/emtricitabine was discontinued in study period 2 (days 11–20). No clinical safety concerns were observed, and it was found that Maraviroc exposure only depends on ritonavir exposure.

2.3 Clinical efficacy and safety

The efficacy of Maraviroc in treating HIV-1 infection was evaluated by a parallel, randomized, two double-blind, and placebo-controlled Phase III studies: MOTIVATE 1 and 2 [14]. MOTIVATE 1 was conducted in Canada and the USA, whereas MOTIVATE 2 was conducted in Australia, Europe and the USA. In this study, 1049 patients were received Maraviroc doses equivalent to 300 mg once daily, 300 mg twice daily, or placebo in a 2:2:1 ratio in addition to optimized background therapy (OBT). The duration of the trial was 48 weeks.

Maraviroc treatment had a significantly better virological and immunological response at week 48 compared with placebo. There is an approximately 1 log₁₀ decrease in HIV-1 RNA

levels from baseline in Maraviroc plus OBT group as compared with OBT alone ($p<0.001$). Viral load was undetectable (<50 copies/mL) in participants treated with Maraviroc once or twice daily compared with patients receiving placebo ($p<0.001$). The CD4 cell count was significantly higher in the Maraviroc once daily (116 cell/ μ L) and Maraviroc twice (124 cells/ μ L) than in the placebo group (61 cells/ μ L) ($p<0.001$) [14].

The efficacy of Maraviroc was also studied in patients who were infected with dual/mixed X4 viruses. In this study, Maraviroc did not show significant benefit on the virologic outcomes, although the CD4 T cell count was slightly increased in Maraviroc plus OBT arm [38]. In other words, Maraviroc has no benefit to those patients with dual/mixed-tropic virus infection.

The efficacy and tolerability of Maraviroc as part of a variety of cART regimens have been well studied in TE patients with R5 HIV-1 infection in two Phase 2b/3 studies [14, 39, 40]. Additional safety and immunovirologic activity data of Maraviroc in regimens were obtained after newer agents such as darunavir, raltegravir, and etravirine were clinically available [41]. It was found that Maraviroc was well tolerated over 96 weeks as a combination with different agents, and treatment with Maraviroc in combination with OBT was associated with significantly greater immunovirologic activity versus placebo plus OBT [40, 41].

The immunologic effectiveness of Maraviroc-and raltegravir-containing regimens (R+M+) versus raltegravir-based regimens containing no Maraviroc (R+M-) were compared, and no difference was observed in terms of the rate of change in CD4 count over 24 months of follow-up [42]. The results contribute to the knowledge regarding the optimal use of Maraviroc in the treatment of HIV-infected patients from an immunological perspective [42].

Maraviroc and raltegravir are new antiretroviral drugs for treating HIV infection, and their uses are important in patients with intolerance or resistance to other antiretroviral agents. The correlation was evaluated between a short therapeutic regimen (raltegravir, Maraviroc, and a protease inhibitor fosamprenavir) and liver diseases. The serum creatine kinase level increased overwhelmingly during the treatment. However, no information is available regarding this correlation [43].

Salvage therapy with raltegravir, Maraviroc and etravirine regimen showed excellent CD4 recovery and HIV-RNA suppression at 24 weeks. This combination regimen treatment is safe and efficacious in the management of drug-experienced patients [43].

Overall, the safety profile of Maraviroc in clinical trials was acceptable. There were no significant differences in liver functional abnormalities between the study arms in the MOTIVATE trials. The most common adverse events, such as diarrhea, fatigue, fever, headache, nausea and upper respiratory, were not found in the Maraviroc arms.

2.4 Resistance

There are two possible ways in which HIV-1 can escape the effect of Maraviroc: X4 variants bening already in the virus population that could result in a HIV coreceptor switch; viral R5 tropism mutations that permit CCR5 binding despite the presence of Maraviroc [44, 45]. The

main mechanism of Maraviroc resistance was found to be that the resistant virus can use Maraviroc-bound CCR5 receptor as a result of selection of multiple mutations in the V3 loop of gp120 [46]. Given that Maraviroc-resistant HIV-1 can bind to CCR5 in both the normal conformation and the maraviroc-bound conformation, increasing the dose of Maraviroc does not increase the inhibition of HIV. This intrinsic viral resistance to the drug is uncommon, and it is not easy to give a recommendation in clinical trials for characterizing Maraviroc resistance. Thus, testing viral tropism is important when Maraviroc is considered as an alternate drug in anti-HIV treatment.

2.5 Applications in Combination Therapy

Maraviroc was studied to substitute the third drug of antiretroviral treatment in aviraemic subjects infected with R5 HIV, and it was found switching the third drug to Maraviroc was safe, efficacious, and with improved lipid parameters [47].

Maraviroc was used in combination with tacrolimus in the setting of post-hepatic transplantation. Although it was just one clinical application, there were emerging data supporting the potential use of Maraviroc for prolonging graft survival [48].

A study in mice showed Maraviroc could reduce the atherosclerotic progression, and reversed the proinflammatory profile in mice with ritonavir-induced inflammation [49]. Although large clinical studies are needed, it is fair to say Maraviroc could benefit HIV-positive patients with residual chronic inflammation [49].

Diaz-Delfin et al. studied the effects of Maraviroc during and after the differentiation of human adipocytes in culture, and they concluded that Maraviroc did not alter adipocyte differentiation, but showed anti-inflammatory properties, which suggested that Maraviroc could be beneficial by minimizing adverse effects on adipose tissue development, metabolism, and inflammation [50].

2.6 Interaction between alcohol and Maraviroc

Many HIV patients think they should not take medication when they drink alcohol. However, resistance could be developed after frequently missed medication. The study from Gruber et al showed that alcohol did not affect Maraviroc pharmacokinetics, so patients should not miss Maraviroc treatment even though alcohol is consumed [51].

2.7 Studies in HIV-2 Treatment

HIV-2 infection undergoes a long asymptomatic phase and AIDS development. Maraviroc is active *in vitro* against CCR5-tropic HIV-2 [52, 53]. Visseaux and coworkers the first time assessed that Maraviroc is active *in vitro* against R5 HIV-2 clinical isolates through a phenotypic peripheral blood mononuclear cell-based test [52]. Borrego and coworkers studied the susceptibility of primary HIV-2 to Maraviroc along with entry inhibitors. They found reduced sensitivity of R5 variants to Maraviroc, indicating that higher dosages of Maraviroc might be needed for the treatment of HIV-2 than HIV-1, and the treatment should be adjusted to the HIV-2 disease courses. There is a growing interest in using Maraviroc to treat HIV-2-infected patients. Maraviroc was combined with foscarnet as a salvage therapy

in HIV-2-infected patients with antiretroviral treatment failure [54]. Armstrong-James et al reported that an HIV-2 patient responded positively to a raltegravir- and Maraviroc-based therapy, while resistant to protease inhibitor, nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) [55]. Caixas et al described a long-term successful control of one HIV-2-infected patient using Maraviroc [56].

2.8 Application in Microbicide Development

An effective vaginal microbicide can reduce HIV-1 transmission to women. Maraviroc is a highly potential microbicide candidate in clinical development. Veazey et al firstly tested the ability of Maraviroc as a vaginal microbicide to prevent transmission using a stringent model that involves challenge of rhesus macaques with a high dose of SHIV-162P3, a CCR5-using virus [57]. Maraviroc provided dose- and time-dependent protection against challenge with SHIV-162P3. The pharmacokinetics and efficacy were assessed, and a high degree of correlation between PK and efficacy was observed [58]. Later, Neff et al. tested Maraviroc as microbicide in RAG-hu humanized mouse model [59]. Female RAG-hu mice were challenged vaginally with HIV-1 after intravaginal application of the maraviroc gel. It was found that Maraviroc gel treated mice were fully protected against HIV-1 challenge, while the placebo gel treated mice all became infected [59]. Their findings demonstrated Maraviroc as a candidate in the development of vaginal microbicides [57, 59].

Malcolm et al. [60] described the sustained release of Maraviroc from matrix-type silicone elastomer vaginal rings after tests in aqueous gel formulations [58]. Their founding could help design macaque challenge experiments and ring performance during human female menstrual cycle [60].

Fetherston et al. reported a combination microbicide formulation containing both dapivirine and Maraviroc, in the form of a silicone elastomer vaginal ring [61]. A silicone elastomer matrix-type ring vaginal formulation containing 25 mg dapivirine and 100 mg Maraviroc has been developed and evaluated in Phase I clinical trial [61]. Maraviroc, combined with dendrimers, showed synergistic profile against CCR5 and dual tropic HIV-1 [62]. Vaccines and microbicides containing Maraviroc may protect better when used together than separately [63]. These evaluations supported the development of combinatorial microbicides to fight against HIV spread.

In Summary, Maraviroc is a potent new antiretroviral drug that has no cross-resistance with other drugs. It is also a valuable drug additional to the current drugs available in the combination against HIV.

Conclusions

Maraviroc is the only HIV-1 CCR5-based entry inhibitor to date approved by FDA. The study of its clinical benefits is still continuing. In this article, we reviewed the medicinal chemistry and clinical applications of Maraviroc as an anti-HIV drug. We also reviewed the development of Maraviroc as a microbicide. Ongoing research and development of Maraviroc-derivatives have showed improved potency and pharmacokinetics over

Maraviroc, suggesting that similar class of CCR5 inhibitors will likely in clinical treatment of HIV infection in the near future.

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Figure 1.
Structure of Maraviroc

Figure 2.
Compound 1 & 2 Structures

Figure 3.
Structures of Compounds **15** and **16**.

Figure 4.
4,4-Disubstituted cyclohexylamine based CCR5 antagonists SAR Study.

Figure 5.
Structure of Compound **28**

Figure 6.
Structures of Compound **29**& **30**

Figure 7.
Structures of Compound **31** & **32**

Table 1

MIP-1 β inhibitory activity and antiviral activity of compound **3–6**.

Compound	MIP-1 β IC ₅₀ (nM)	Antiviral activity
3	45	210 nM IC ₅₀
4	40	75 nM IC ₅₀
(<i>s</i>)- 4	20	73 nM IC ₅₀
5	2	13 nM IC ₉₀
6	6	3 nM IC ₉₀

Table 2Antiviral activity and hERG channel activity of compound **7**, **8** and Maraviroc.

Compound	Antiviral IC ₉₀ (nM)	hERG channel inhibition
7	39	70% @ 300 nM
8	8	30% @ 300 nM
Maraviroc	2	0% @ 300 nM

Table 3Cell fusion and antiviral activities for maraviroc and related analogues **9–12**.

Compound	Fusion IC ₅₀ ^a	AV IC ₉₀ ^b
Maraviroc	0.2 nM	0.7 nM
9	7.5 nM	Inactive
10	14 nM	–
11	48 nM	310 nM
12	5 nM	–

^a Cell fusion assay^b Antiviral activity-concentration required to inhibit replication of HIV_{Bal} in PM-1 cells by 90%

Table 4Activities of compounds **13** and **14**.

13 14				
Compound	Fusion IC ₅₀ nM	logD _{7.4}	HLM (μl/min/mg of microsomal protein)	hERG IC ₅₀ nM
13	37.5	1.2	<7	849
14	2.0	1.9	<7	4000

Table 5

RANTES binding inhibition and antiviral activity of exo- **15(a–d)**, endo- **15(a–d)**, and **16(a–d)**.

Compound	Binding (nM) ^a	Antiviral (nM) ^b
Maraviroc	1.4	2.8
Exo- 15a	35	40
Exo- 15b	6	200
Exo- 15c	43	625
Exo- 15d	–	81
Endo- 15a	18	210
Endo- 15b	6	74
Endo- 15c	30	625
Endo- 15d	8	41
16a	7	62
16b	5	24
16c	13	220
16d	5	5

^a Binding inhibition (IC₅₀) of [¹²⁸I]-RANTES to CCR5-expressing CHO cells.

^b Replication inhibition (IC₅₀) of R5 HIV_{NL}BaI in JC53-BL cells.

Table 6

IC₅₀ values for compounds **17–20** in a MIP 1-β binding assay.

<p>17: n = 1 18: n = 2</p> <p>19: R = H 20: R = CH₃</p>	
Compound	IC ₅₀ (μM)
17	0.97
18	0.31
19	0.031
20	0.004

Viral entry inhibition of compounds **20–24**, IC₅₀ (μM).

Compound	Virus				
	JRCSF	ASM80	Ba-L	97-ZA-003	RU570
20	0.118	0.058	0.048	0.029	0.028
Maraviroc	0.005	0.006	0.004	0.008	0.002
21	0.009	0.016	0.028	0.009	0.005
22	0.009	0.011	0.062	0.017	0.007
23	0.015	0.120	1.048	0.116	0.090
24	0.003	0.005	0.008	0.005	0.002

Table 8

Activities of compounds **25–27**.

Compound	pIC50 CCR5 binding [MIP-1β]	Ba-L-Hos pIC50	hERG patch clamp pIC50	QTc (%)	RAT PO DNAUC [ng.h/mL]	DOG PO DNAUC [ng.h/mL]
25	7.8	7.80	5.7	9.4	16	-
26	9.45	8.01	6.0	6.5	144	-
27	8.37	8.46	4.72	1.2	272	170

Table 9

Profiles of **30** and Maraviroc

Compound	Antiviral Activity		Pharmacokinetic property		Human, Rat, Dog Liver microsome Assays			hERG channel activity	Permeability
	Gp 160 IC ₅₀ (nM)	AV IC ₉₀ (nM)	Rat absorption	Dog absorption	HLM Cl _{int}	RLM Cl _{int}	DLM Cl _{int}		
Maraviroc	0.2	3.2	20	70	49	< 6	< 9	0% @ 300 nM	< 1/12
30	< 0.1	2.0	complete	complete	7	< 6	< 9	IC ₅₀ 12 μM	2/8