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Miniperspective

Discovery and Development of Small-Molecule Chemokine Coreceptor CCR5 Antagonists

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Introduction

Human immunodeficiency virus (HIV) infection with its clinical progression to AIDS has become one of the fatal diseases in the world and the leading cause of death in Africa.[1] Over 40 million people worldwide are infected with HIV.[2] Great progress has been made over the past decade in reducing HIV-related mortality and morbidity by treating infected individuals with highly active antiretroviral therapy (HAART), which is a combination of drugs targeting one or more steps in the viral life cycle.[3] However, complicated dosing regimens of the current therapy, coupled with side effects of the component drugs, have led to diminished adherence.[4] Many patients failing to achieve sustained suppression of viral replication and the emergence of drug-resistant strains of HIV have become critical issues in public health.[5,6] Hence, there is a compelling need to discover new drugs or targets for therapeutic intervention.[7−9]

The process of HIV-1 entry into host cells is an attractive target for antiretroviral intervention.[10] It has been known for a long time that the HIV gp120 envelope protein binds to the CD4 receptor on T-cells and macrophages to start the infection process.[11] Some of the subsequent steps, which are essential for viral entry after HIV docks on to the CD4 receptor, were elucidated during the middle 1990s. Following HIV binding to CD4 a conformational change in the gp120 envelope protein occurs, which allows it to bind a second receptor on the host cell. The chemokine receptors CCR5 and CXCR4 were identified to be the essential coreceptors for HIV-1.[12] The coreceptor engagement causes a second conformational change in the HIV envelope, this time in the gp41 protein, revealing a peptide that fuses the HIV envelope with the host cell membrane.[9] The potential for entry inhibitors to be useful drugs was first established by the peptide inhibitor T-20, which blocks the conformational changes in HIV-1 gp-41 that are necessary for virus-cell fusion.[13] Although efficacious, this inhibitor is a polypeptide requiring parenteral administration and is produced by an admirable yet expensive synthetic route. Another plausible site for pharmacological intervention in the HIV entry process is the interaction between HIV-1 gp-120 and the chemokine coreceptor CCR5. This Miniperspective will focus on the discovery and development of novel, orally active, small-molecule CCR5 chemokine receptor antagonists.[14]

Background

The endogenous ligands for CCR5 are the proinflammatory peptides called chemokines (e.g., RANTES, MIP-1α, and MIP-1β). The recombinant and synthetic forms of RANTES suppress HIV-1 replication in cell culture in a dose-dependent manner.[15] In addition, the experimental knockout of CCR5 in mice has a benign phenotype, but some studies suggest altered immune function in some challenge models.[16] Together, these studies suggested that CCR5 blockade is a plausible mechanism for inhibiting HIV-1 from cell entry. While the discovery of a new target was exciting because there are fewer propensities for mutation in the host cell than in the virus, this was tempered with caution that turning off an immune system receptor might have some deleterious effect. However, in 1996 Liu et al. reported that a natural genetic absence of CCR5 (the CCR5-Δ32-homozygous genotype) was detected in apparently healthy individuals and that this mutation was strongly protective against HIV-1 infection.[17] Furthermore, heterozygous individuals who express only one CCR5 allele were found to have slower progression to AIDS compared to patients having no deletion.[18] Hence, an antagonist that is specific for CCR5 may cause few, if any, mechanism-based side effects. From an antiviral perspective, CCR5 is the coreceptor used by the R5-tropic HIV-1 strains, which predominate during the early stages of HIV-1 infection.[19] As the disease progresses, the viruses capable of

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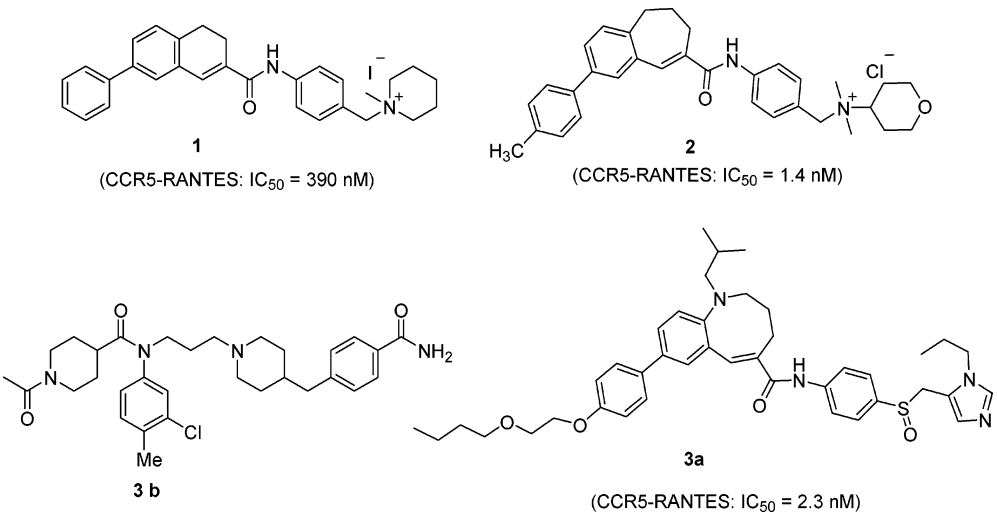
Chart 1. Anilide Derivatives as Small-Molecule CCR5 Antagonists



using the CXCR4 receptor (X4-tropic) begin to appear in greater frequency, often heralding the onset of AIDS. However, in a majority of cases, many patients succumb to the R5 virus without a change in tropism to the X4 form.[20] Thus, the CCR5 receptor that hosts the R5-tropic HIV-1 strain attracted many research groups to design small molecules that would bind to it and inhibit the virus.[14] There is concern that the inhibition of the R5-tropic HIV-1 by blocking the CCR5 receptor would prompt an earlier switch to the X4-tropic strain and thereby accelerate the disease. Passage experiments with known CCR5 antagonists have shown that the tropism switch is not necessary for development of resistance.[21]

The CCR5 receptor is a member of the G-protein-coupled receptor (GPCR) superfamily. The GPCRs are transmembrane polypeptides that typically contain seven loops and mediate various intracellular events when triggered by extracellular ligands. In the years preceding the discovery of CCR5 as an essential HIV coreceptor, many pharmaceutical laboratories had amassed several libraries of compounds directed at inhibiting GPCRs (e.g., NK1-3, NPY, M1-M5, etc.) for potential treatment of various diseases.[22] These collections were screened rapidly against the newly discovered HIV coreceptor, allowing the discovery of lead compounds based on privileged structures and the initiation of lead optimization efforts. The following account is a brief summary of the tremendous amount of work on CCR5 antagonists reported by various research groups.

Summary of Studies on CCR5 Antagonists

The first small-molecule CCR5 antagonist published in the scientific literature was TAK-779 (**2**, Chart 1) from Takeda Chemical Industries Ltd.[23a,b] The antagonist **2** was discovered after chemical optimization of initial lead quaternary ammonium salt **1** from a high-throughput screening receptor binding assay. Compound **2** exhibited potent activity against R5 HIV-1 in vitro. However, the development of **2** was discontinued because of toxicity at the injection site. Replacement of the quarternary ammonium moiety of **2** with a polar sulfoxide and ring expansion to (6, 8) fused nuclei as well as substitution of 4-(2-butoxyethoxy) group for methyl resulted in **3a** (TAK-652) with an increase in both potency and oral bioavailability.[23e] This antagonist was active against R5 HIV-1 clinical isolates containing reverse transcriptase and protease inhibitor-resistant mutations, with a mean EC_{50} and EC_{90} of 0.061 and 0.25 nM, respectively. A single administration of **3a** up to 100 mg was safe and well tolerated in humans. This antagonist also displayed favorable pharmacokinetics in humans. The clinical efficacy of **3a** in HIV-1 infected individuals has not been reported. Takeda also discussed another orally available CCR5 anatgonist **3b** (TAK-220),[23c] which inhibits the replication of R5 HIV-1 isolates with an EC_{50} of 1.1 nM. [23d]

Two structurally related classes of CCR5 anatgonists were developed by researchers at Schering-Plough, one containing a piperdino-piperdine core structure as in **6** and another with a piperazino-piperdine core (**7**, vide infra). The initial leads for the both classes came from screening of Schering-Plough in-house compound collections. The structure of the initial lead for the piperidino-piperidine series is antagonist **4** as shown in Chart 2. The medicinal chemistry optimization of antagonist **4**, focusing mainly on improving the potency and selectivity versus the muscarinic receptor (M2) afforded antagonist **5**. Introduction of oxime at the benzylic position coupled with replacement of 2,6 dimethylbenzamide with 2,6-dimethylnicotinamide *N*-oxide afforded anatagonists with an improved pharmacokinetic profile in addition to antiviral activity.[24a,b]

CCR5 antagonist **6** (SCH-C) was selected as Schering-Plough's first clinical candidate because of its excellent antiviral activity and pharmacological profile and **6** was the first CCR5 antagonist to advance to clinical efficacy studies. The inhibitor **6** was safe and generally well tolerated, although cardiac side effects (QTc interval prolongation) were noted at the highest dose tested (400 mg twice daily). The antagonist **6** demonstrated a clear antiviral effect in HIV-1 infected individuals in a phase 1b study. At a dose of 25 mg twice daily, antagonist **6** exhibited a >0.5 log drop in viral load in 10 out of 12 subjects and >1 log reduction in four subjects. However, two subjects showed no significant reduction in viral load, a result that could be due to the presence of a CCR5 variant in these individuals that is not blocked by antagonist **6**.[24c]

The high-throughput screening hit in the piperazine series was compound **7** (Chart 3), a potent muscarinic M2 antagonist with modest CCR5 affinity.[25a] Truncation of the left side leaving a small para substituent on the phenyl ring and the discovery of a key pharmacophore element in the form of the 2(*S*)-methylpiperazine gave the initial lead **8**. This inhibitor had high affinity for CCR5 and essentially no activity at the muscarinic receptors but suffered from poor oral bioavailability in rat. Further optimization of the lead **8**, focusing on improving oral pharmacokinetics, led to the nictotinamide **9** (AD-101).

The oral bioavailability for **9** in rat was still modest primarily because of its rapid in vivo metabolism to the corresponding

Chart 2. Oximino-piperidino-piperidine Derived CCR5 Anatgonists

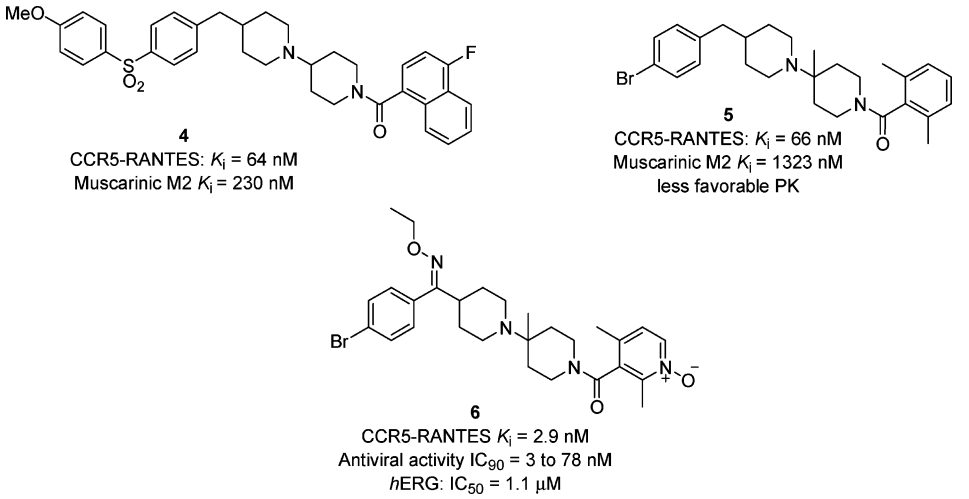
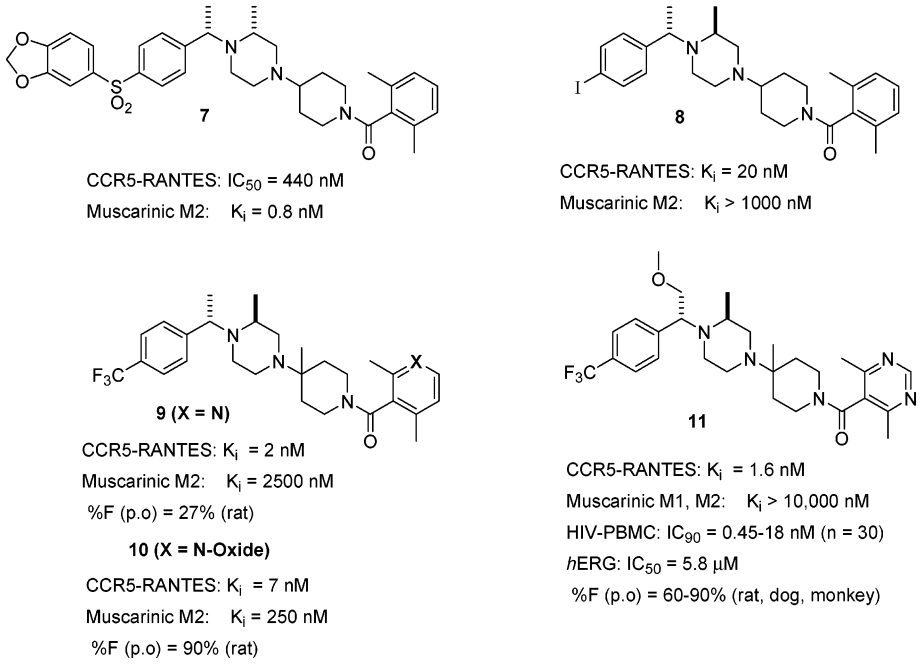


Chart 3. Chiral Piperazine-Based CCR5 Antagonists

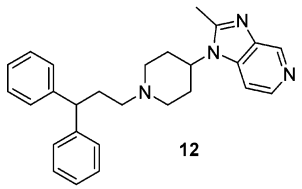


N-oxide (**10**). Metabolite **10** was a potent binder at CCR5, thereby inhibiting HIV-1 entry into cells, and significantly improved oral bioavailability in rat, dog, and monkey.[25b] However, the selectivity for CCR5 over the muscarinic receptors, particularly M2, was greatly diminished. The high oral blood levels, combined with appreciable levels of activity at the M1 and M2 muscarinic receptors, which are prevalent in the heart and intestinal tissue, led to the observation of undesirable cardiovascular and gastrointestinal side effects during ancillary pharmacology studies in rat. Furthermore, the presence of the unsymmetrical tertiary nicotinamide *N*-oxide moiety in structures such as **9** and **10** gave rise to the observation of four rotomers for these compounds.[25c]

Although neither antagonist **9** nor **10** could be advanced further, they served as valuable tools to elucidate mechanistic and structural aspects of CCR5 antagonism. After the passage of primary R5 HIV-1 isolate 19 times in cell cultures with antagonist **9**, an escape mutant emerged that was insensitive to **9** and cross-resistant to **6**. However, the escape mutant was not X4-tropic, suggesting that it may be binding to the drug/coreceptor complex.[20] In another study, details of the small-molecule binding pocket of CCR5 were reported. Since there is no X-ray crystal structure for the membrane-bound CCR5 receptor, these studies were based on its homology with bacterial rhodopsin. When a site-directed mutagenesis approach and the HIV-1infection-based assay were used, it was shown that the CCR5 antagonists **2**, **6**, and **9** bind to very similar sites on CCR5, located within a cavity near the extracellular surface of the receptor formed by transmembrane helices H1−H3 and H7. The N-terminus and the extracellular loops (E1−E3) are not involved in binding to these antagonists.[26]

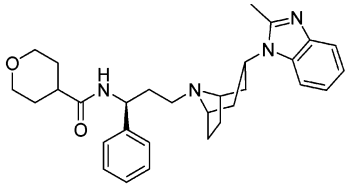
In a backup program to address the issues in the piperazine series, the 4,6-dimethylpyrimidine-5-carboxamide was discovered as a suitable replacement for the nicotinamide *N*-oxide present in **10**, because it has only two rapidly equilibrating rotomers, while maintaining CCR5 affinity and anti-HIV activity coupled with good oral bioavailability.[25c] The key to the receptor selectivity issue (CCR5 vs M1/M2) in the piperazine series lay in finding the optimal benzylic substituent. While a propyl group at the benzylic position showed significant improvement over the benzylic methyl analogue in its CCR5/M1−M2 receptor selectivity and had excellent potency in antiviral assays, it

Chart 4. Discovery of Tropane-Based CCR5 Antagonist **15** from High-Throughput Screening Hit **12**



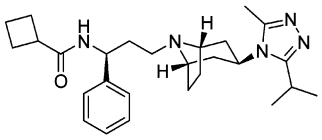
12

MIP-1β IC50 = 4 nM
No antivial activity
CYP 2D6 IC_{50} = 40 nM



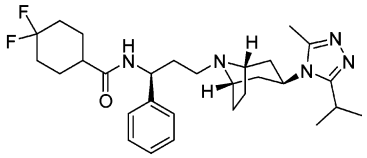
13

antiviral activity IC_{90} = 0.6 nM
less favorable PK



14

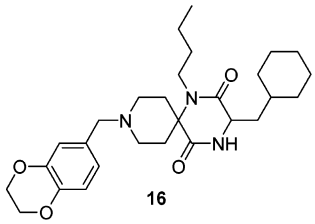
MIP-1β IC50 = 7 nM
antiviral activity IC_{90} = 8 nM
high QTC risk potential



15

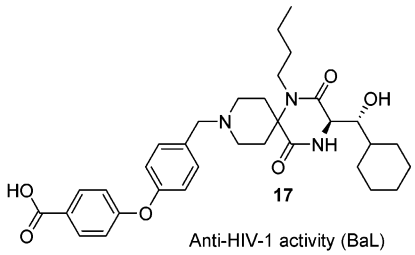
MIP-1β IC50 = 2 nM
antiviral activity mean IC_{90} = 1 nM

Chart 5. Spirodiketopiperazine-Based CCR5 Inhibitors



16

Anti-HIV-1 activity (BaL)
IC_{50} = 40 nM



17

Anti-HIV-1 activity (BaL)
IC_{50} = 0.5 nM

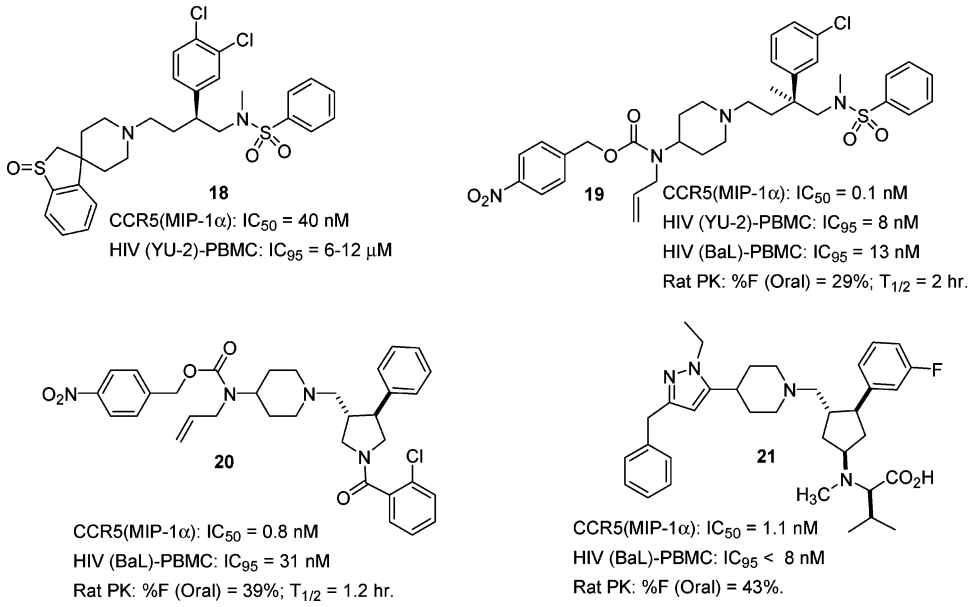
formed an acyl glucuronide via oxidation of the benzylic propyl group and also had moderate hERG activity. A search for isosteric replacements for the *n*-propyl group identified CCR5 antagonist **11** (*Vicriviroc*, Sch-417690, Sch-D).[25d] Preclinically, **11** had excellent potency against R5-tropic HIV and very good oral bioavailability in rat and monkey. The enhanced selectivity for CCR5 over the muscarinic receptors and hERG was reflected in a much improved side effect profile during safety pharmacology evaluation.[25e] In clinical studies, antagonist **11** was well tolerated up to 50 mg b.i.d. and produced up to 1.6 log reduction in HIV load at doses of 25 and 50 mg b.i.d. in treatment naive HIV infected individuals.[25f]

Researchers at Pfizer Inc. have identified a piperidine-based CCR5 inhibitor **15** (Maraviroc, UK-427,857) (Chart 4), which is currently in phase III clinical trials.[27a] Pfizer's CCR5 program was initiated from the hit **12**, identified from a high-throughput screen. Initial optimization to resolve cytochrome P450 2D6 inhibition and lack of antiviral activity associated with antagonist **12** led to tropane-derived amide analogue **13**. The potent and selective CCR5 inhibitor **13** exhibited high human and dog hepatocyte clearance (14 and 27 mL min^{-1} kg^{-1}). Further optimization of antagonist **13** resulted in **14** with favorable pharmacokinetics. Unfortunately, **14** did not provide desirable safety window in terms of QTc threshold. Further modification of the cyclobutylamide portion of **14** led to clinical compound **15**. This antagonist exhibited an excellent potency against a wide range of primary isolates utilizing CCR5 for cell entry with IC_{90} ranging from 0.5 to 13.4 nM ($n = 43$).[27b] At a dose of 25 mg once a day, compound **15** produced 0.4 log reduction in viral load, and at dose of 100 mg twice a day, compound **15** achieved a mean 1.4 log reduction from baseline. Antagonist **15** was well tolerated with no serious adverse events.[27c]

Spirodiketopiperazine **17** (Aplaviroc, ONO-4128, GW873140) (Chart 5) is another important class of low molecular weight CCR5 inhibitors, disclosed by Ono Pharmaceuticals.[28a] Antagonist **17** showed high potency in the MIP-1α binding assay and inhibited replication of R5 viruses in the cell assay with an IC_{50} of 30−60 nM. This antagonist also did not inhibit X4-trpic strains of HIV-1, which utilize CXCR4 receptors for entry, confirming its selectivity for the CCR5 receptor. Antagonist **17** was then developed following initial promising results with antagonist **16**.[28b] CCR5 antagonist **17** demonstrated a 2-fold increase in activity against HIV-1 isolates over antagonist **16**. At a dose of 600 mg twice a day for 10 days, antagonist **17** produced a mean viral load reduction of 1.5 log_{10}.[28c] Recently, it was announced that clinical studies of **17** have been discontinued because of idiosyncratic hepatotoxicity only seen in 1% of patients.

In an extensive series of papers, research groups at Merck have described their proprietary CCR5 antagonists based on acyclic and cyclic scaffolds.[29] Their early work stemmed from compound **18** (Chart 6) with its *N*-methylbutane amine core structure bearing a spirocyclic piperidine at the 4-position and an (*S*)-phenyl moiety at the 2-position. The secondary amine itself was capped with benzene sulfonamide, which was found to be optimal. This lead had modest affinity for CCR5 in the binding assay but weak antiviral activity in a PBMC-based HIV infectivity assay. Lead optimization studies produced antagonist **19**, which had high potency in the binding and cell-based assays. Additionally **19** had good oral bioavailability in rat, although the bioavailability was reduced in dog. Rational drug design via locking of the active conformation led to the novel 1,3,4-trisubstituted pyrrolidine scaffold exemplified by compound **20**. While the SAR with respect to the piperidine 4-substituent

Chart 6. Acyclic and Cyclic Scaffold Based CCR5 Antagonists



paralleled the acyclic series, the N-atom, now locked in a pyrrolidine ring, tolerated a wide range of substituents, with a 2-chlorobenzoyl group being optimal. The pyrrolidine scaffold gave rise to the cyclopentane template depicted in structure **21**. In an efficacy model study, **21** (code name of cmpd-167) showed significant reduction in viral load in rhesus macaques infected with simian immunodeficiency virus (SIV). However, antagonist **21** is not being pursued further as a potential anti-HIV agent. By application of site directed mutagenesis coupled with the molecular modeling technique, it has been proposed that the acyclic butane amine and the 1,3,4-trisubstituted pyrrolidine based CCR5 antagonists described above bind in a cleft formed by transmembrane helices 2, 3, 6, and 7. Interestingly, the 2-phenyl substituent in structures such as **19** and the 3-phenyl substituents in structures such as **20** fit in an aromatic pocket formed between helices 3 and 6; the N-1 substituent in **20** occupies the same pocket formed by helices 2, 3, and 7 that is filled by the sulfonamide group in **19**.

Conclusion

The keys to success in the discovery of new drugs are a valid biological target, a viable chemical lead with scalable synthetic routes, reliable efficacy models, and the availability of tractable pharmacodynamic markers. Many of these factors converged nicely in the case histories of the CCR5 antagonists discussed above, resulting in nearly all of them advancing into clinical trials. Rapidly establishing proof of concept and identifying critical issues such as QT_c prolongation or hepatotoxicity helped in addressing these issues in backup programs. Medicinal chemistry played a pivotal role, bridging virology and pharmacology through the development of consistent structure−activity and structure−pharmacokinetic relationships. There are still various challenges and unknowns associated with CCR5 inhibitors such as drug resistance, viral tropism. and possible long-term adverse events. At the time of this writing, additional CCR5 antagonists have been announced to be entering clinical trials, but no further information on these antagonists has been reported. It is hoped that some of these will achieve success in the clinic and become approved drugs for treating HIV infection and other diseases.

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Biographies

Anandan Palani received his Ph.D. in 1994 from University of Utah at Salt Lake City under the supervision of Prof. Gary E. Keck. His postdoctoral training occurred at Harvard University, Cambridge, MA, under the direction of Prof. E. J. Corey. In 1996 he joined Schering-Plough Research Institute, where he is currently Associate Director of Medicinal Chemistry. In addition to the CCR5 program, his research interests at Schering-Plough include potential treatments for metabolic and central nervous system disorders.

Jayaram R. Tagat received his Ph.D. in 1984 from the University of Rochester, working in the laboratories of Prof. R. K. Boeckman, Jr., and carried out postdoctoral studies with Prof. M. E. Kuehne at the University of Vermont in Burlington. In 1985 he joined Schering-Plough Research Institute, where he is currently a Research Fellow. His research interests include programs in the areas of antibacterials, antiviral therapy, central nervous system disorders, and oncology.

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